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(c) 2006 CAB International
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7.

Set	Items	Description
?	s	(sialyl adj transferase) (s) inhibit?
Processing		
Processed 10 of 40 files ...		
Processing		
Completed processing all files		
	0	SIALYL ADJ TRANSFERASE
	8640349	INHIBIT?
	S1	0 (SIALYL ADJ TRANSFERASE) (S) INHIBIT?
?	s	(sialyl transferase) (s) inhibit?
Processing		
Processed 20 of 40 files ...		
Completed processing all files		
	267	SIALYL TRANSFERASE
	8640349	INHIBIT?
	S2	0 (SIALYL TRANSFERASE) (S) INHIBIT?
?	s	(sialic acid transferase) and inhibit?
Processing		
Processed 20 of 40 files ...		
Completed processing all files		
	1	SIALIC ACID TRANSFERASE
	8640349	INHIBIT?
	S3	0 (SIALIC ACID TRANSFERASE) AND INHIBIT?
?	s	(sialyl transferase) and inhibit?
Processing		
Processed 10 of 40 files ...		

Processing

Completed processing all files

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      267  SIALYL TRANSFERASE
      8640349  INHIBIT?
S4      21  (SIALYL TRANSFERASE) AND INHIBIT?
? rd
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S5      20  RD  (unique items)
? show files;ds;t/3,k/all
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File 143: Biol. & Agric. Index 1983-2006/Feb
      (c) 2006 The HW Wilson Co
File 144: Pascal 1973-2006/Feb W1
      (c) 2006 INIST/CNRS
File 155: MEDLINE(R) 1951-2006/Feb 28
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File 172: EMBASE Alert 2006/Mar 01
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File 358: Current BioTech Abs 1983-2005/Dec
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      (c) 2006 Reed Business Information Ltd.
File 370: Science 1996-1999/Jul W3
      (c) 1999 AAAS
File 399: CA SEARCH(R) 1967-2006/UD=14410
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 File 164:Allied & Complementary Medicine 1984-2006/Mar
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 File 444:New England Journal of Med. 1985-2006/Feb W2
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Set	Items	Description
S1	0	(SIALYL ADJ TRANSFERASE) (S) INHIBIT?
S2	0	(SIALYL TRANSFERASE) (S) INHIBIT?
S3	0	(SIALIC ACID TRANSFERASE) AND INHIBIT?
S4	21	(SIALYL TRANSFERASE) AND INHIBIT?
S5	20	RD (unique items)

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5/3,K/1 (Item 1 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
 (c) 2006 BIOSIS. All rts. reserv.

0013628032 BIOSIS NO.: 200200221543

Redistribution of membrane proteins between the Golgi apparatus and endoplasmic reticulum in plants is reversible and not dependent on cytoskeletal networks

AUTHOR: Saint-Jore Claude M; Evins Janet; Batoko Henri; Brandizzi Federica; Moore Ian; Hawes Chris (Reprint)

AUTHOR ADDRESS: School of Biological and Molecular Sciences, Oxford Brookes University, Headington, Oxford, OX3 0BP, UK**UK

JOURNAL: Plant Journal 29 (5): p661-678 March, 2002 2002

MEDIUM: print

ISSN: 0960-7412

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

...ABSTRACT: brefeldin A (BFA) resulted in the reversible redistribution of ST-GFP into the endoplasmic reticulum. This effect occurred in the presence of a protein synthesis *inhibitor* and also in the absence of

microtubules or actin filaments. Likewise, reformation of Golgi stacks on removal of BFA was not dependent on either protein...
...These data suggest that ER to Golgi transport in the cell types observed does not require cytoskeletal-based mechanochemical motor systems.
However, expression of an *inhibitory* mutant of Arabidopsis Rab 1b (AtRab1b(N121I)) significantly slowed down the recovery of Golgi fluorescence in BFA treated cells indicating a role for Rab1 in...
...REGISTRY NUMBERS: *sialyl transferase*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*sialyl transferase*

5/3,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0007870589 BIOSIS NO.: 199192116360
***INHIBITION* OF SIALYL TRANSFERASE ACTIVITY BY GOSSYPOL ACETIC ACID IN HUMAN SEMINAL PLASMA**
AUTHOR: LEVINSKY H (Reprint); SINGER R; SAGIV M; LEHRER N; ALLALOUF D
AUTHOR ADDRESS: MALE FERTILITY LAB, BEILINSON MED CENT, PETAH TIKVA 49 100, ISRAEL**ISRAEL
JOURNAL: Andrologia 23 (2): p159-162 1991
ISSN: 0303-4569
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

***INHIBITION* OF SIALYL TRANSFERASE ACTIVITY BY GOSSYPOL ACETIC ACID IN HUMAN SEMINAL PLASMA**

...ABSTRACT: 61.3 +- 8.0%-67.7 +- 8.9% of the activity obtained by incubation with BWB only GAA was found to exert a dose-dependent *inhibition* of S.T. activity, ranging from 38.3 +- 20.6% to 53.4 +- 19.4% (with 25 .mu.g) and from 11.3 +- 14.8...
...REGISTRY NUMBERS: *SIALYL TRANSFERASE*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0005804280 BIOSIS NO.: 198834033171
MONENSIN SPECIFICALLY *INHIBITS* AN INTERMEDIATE STEP IN THE GLYCOSYLATION OF THE SIALOMUCIN ASGP-L
AUTHOR: SPIELMAN J (Reprint); HULL S R; CARRAWAY K L
AUTHOR ADDRESS: UNIV MIAMI SCH MED, MIAMI, FLA, USA**USA
JOURNAL: Journal of Cell Biology 105 (4 PART 2): p81A 1987
CONFERENCE/MEETING: TWENTY-SEVENTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY, ST. LOUIS, MISSOURI, USA, NOVEMBER 16-20, 1987. J CELL BIOL.
ISSN: 0021-9525
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

MONENSIN SPECIFICALLY *INHIBITS* AN INTERMEDIATE STEP IN THE GLYCOSYLATION OF THE SIALOMUCIN ASGP-L

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0003999103 BIOSIS NO.: 198376090538
**PHYSIOLOGY OF SIALIC-ACID CAPSULAR POLY SACCHARIDE SYNTHESIS IN SEROGROUP B
NEISSERIA-MENINGITIDIS**
AUTHOR: MASSON L (Reprint); HOLBEIN B E
AUTHOR ADDRESS: DEP MICROBIOL IMMUNOL, MCGILL UNIV, MONTREAL, QUEBEC, CAN
H3A 2B4**CANADA
JOURNAL: Journal of Bacteriology 154 (2): p728-736 1983
ISSN: 0021-9193
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

...ABSTRACT: a Km of 0.88 .mu.M, had a Vmax of 10.75 nmol of NANA
produced/h per mg of protein and was completely *inhibited* of 45.3 .mu.M
CMP. The sialyltransferase, which also had CMP-NANA as substrate, was
insensitive to CMP addition. Subcellular fractionation and purification
of...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0003201573 BIOSIS NO.: 198171020532
**PRESENCE AND REGIONAL DISTRIBUTION OF SIALYL TRANSFERASE IN THE EPIDIDYMIS
OF THE RAT**
AUTHOR: BERNAL A (Reprint); TORRES J; REYES A; ROSADO A
AUTHOR ADDRESS: DIV BIOQUIM, DEP INVEST BIOMED, CMN-INST MEX SEGUR SOC,
APDO 73-231, MEXICO 73, DF, MEX**MEXICO
JOURNAL: Biology of Reproduction 23 (2): p290-293 1980
ISSN: 0006-3363
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

...ABSTRACT: cauda epididymis. Caput spermatozoa were as good sialyl
acceptors as fetuin with caput homogenates and better than fetuin with
cauda homogenates. Cauda spermatozoa behave as *inhibitors* of the
enzymatic activity, particularly with caput extracts. No transferase
activity could be detected in caput spermatozoa in the absence of
epididymal extracts. Cauda spermatozoa...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/6 (Item 6 from file: 5)
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0002950744 BIOSIS NO.: 198069064731

**BIOSYNTHESIS OF HUMAN BLOOD GROUP T SPECIFIC N SPECIFIC AND M SPECIFIC
IMMUNO DETERMINANTS ON HUMAN ERYTHROCYTE ANTIGENS**

AUTHOR: DESAI P R (Reprint); SPRINGER G F

AUTHOR ADDRESS: IMMUNOCHEM RES, EVANSTON HOSP, 2650 RIDGE AVE, EVANSTON,
ILL 60201, USA**USA

JOURNAL: Journal of Immunogenetics (Oxford) 6 (6): p403-418 1979

ISSN: 0305-1811

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: The specificity of this biosynthesis was ascertained by agglutination with human and animal anti-T, by specific absorption of human anti-T and by agglutination *inhibition* assays. With isolated human erythrocyte T antigen as substrate N- and M-specific structures were synthesized with sera from individual human donors in presence of...

DESCRIPTORS: *SIALYL TRANSFERASE*

5/3,K/7 (Item 7 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002750328 BIOSIS NO.: 197968061827

**SIALIC-ACID CONTENT AND GROWTH CONTROL OF MOUSE CELLS TRANSFORMED BY A
TEMPERATURE SENSITIVE MUTANT OF SV-40**

AUTHOR: AOI Y (Reprint)

AUTHOR ADDRESS: INST MED SCI, UNIV TOKYO, PO TAKANAWA, 108 TOKYO, JPN**
JAPAN

JOURNAL: Journal of Medicine (Westbury) 9 (6): p503-510 1978

ISSN: 0025-7850

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: electrofocusing, but when treated with neuraminidase, differences of elution patterns were extinguished. There was a positive correlation between sialic acid content and loss of contact *inhibition* in the cell line examined.

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/8 (Item 8 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002640412 BIOSIS NO.: 197967029407

**BIOCHEMICAL AND ULTRASTRUCTURAL STUDIES OF ECTO GLYCOSYL TRANSFERASE
SYSTEMS OF MURINE L-1210 LEUKEMIC CELLS**

AUTHOR: BERNACKI R J (Reprint); PORTER C W

AUTHOR ADDRESS: DEP EXP THER, GRACE CANCER DRUG CENT, ROSWELL PARK MEML
INST, 666 ELM ST, BUFFALO, NY 14263, USA**USA

JOURNAL: Journal of Supramolecular Structure 8 (2): p139-152 1978

ISSN: 0091-7419

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: N-acetylneuraminic acid is the consequence of a cell surface sialyltransferase system. Pretreatment of cells with the nonpenetrating reagent, diazonium salt of sulfonilic acid, significantly *inhibited* this ectoenzyme system while only marginally affecting galactose uptake and incorporation at the Golgi apparatus. Interestingly, incorporation from CMP-N-acetylneuraminic acid declined as the...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/9 (Item 9 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002275258 BIOSIS NO.: 197814049245

OCCURRENCE OF AN INTRA CELLULAR *INHIBITOR* OF ECTO SIALYL TRANSFERASE IN LYMPHOCYTES

AUTHOR: CACAN R; VERBERT A; HOFACK B; MONTREUIL J

JOURNAL: Febs Letters 81 (1): p53-56 1977

ISSN: 0014-5793

DOCUMENT TYPE: Article

RECORD TYPE: Citation

LANGUAGE: Unspecified

OCCURRENCE OF AN INTRA CELLULAR *INHIBITOR* OF ECTO SIALYL TRANSFERASE IN LYMPHOCYTES

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*

1 5/3,K/10 (Item 10 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002200864 BIOSIS NO.: 197764049220

CELL SURFACE GLYCOSYL TRANSFERASES IN CULTURED FIBROBLASTS INCREASED ACTIVITY AND RELEASE DURING SERUM STIMULATION OF GROWTH

AUTHOR: LAMONT J T; GAMMON M T; ISSELBACHER K J

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 74 (3): p1086-1090 1977

ISSN: 0027-8424

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Unspecified

...ABSTRACT: cells. There was no detectable hydrolysis of UDP-galactose to free galactose by these cells, nor did a 100-fold molar excess of free galactose *inhibit* cell-surface galactosyltransferase. There was a marked increase in specific activity of cell-surface exogenous galactosyltransferase in serum-stimulated as compared to resting fibroblasts. Dividing...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/11 (Item 11 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002191275 BIOSIS NO.: 197764039631

NUCLEOTIDE INDUCED *INHIBITION* OF SURFACE SIALYL TRANSFERASE ACTIVITY ON CULTURED BURKITT'S LYMPHOMA CELLS

AUTHOR: KILTON L J; MACA R D

JOURNAL: Journal of the National Cancer Institute 58 (5): p1479-1481 1977

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Unspecified

NUCLEOTIDE INDUCED *INHIBITION* OF SURFACE SIALYL TRANSFERASE ACTIVITY ON CULTURED BURKITT'S LYMPHOMA CELLS

...ABSTRACT: with neuraminidase increased the labeled sialoprotein severalfold. A number of nucleotides were effective in decreasing the amount of sialoprotein assembly. CMP was the most effective *inhibitor*. UMP, AMP and GMP were also *inhibitory*, but to a lesser degree. The diphosphate derivatives were similarly *inhibitory*, but generally less active than their monophosphate counterparts. The cyclic [c] nucleotides were the least effective of all nucleotides tested. cCMP and cAMP showed a...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/12 (Item 12 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

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0002189501 BIOSIS NO.: 197764037857

GLYCOSYL TRANSFERASE AND UDP GALACTOSE PYRO PHOSPHATASE ACTIVITIES IN THE ENDOMETRIUM DURING THE ESTROUS CYCLE OF THE RAT

AUTHOR: NELSON J D; JATO-RODRIGUEZ J J; LABRIE F; MOOKERJEA S

JOURNAL: Journal of Endocrinology 73 (1): p53-58 1977

ISSN: 0022-0795

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Unspecified

...ABSTRACT: on the morning of proestrus, reaching a peak on the morning of estrus. Previously, it was shown that estradiol administration stimulated galactosyl- and sialyltransferase and *inhibited* pyrophosphatase activities several-fold in the endometrium of ovariectomized rats. Progesterone prevented estradiol effect on the enzymes. Changes in glycosyltransferase and pyrophosphatase activities during the...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/13 (Item 13 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

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0002161211 BIOSIS NO.: 197764009567

THE EFFECTS OF CMP ON THE REGENERATION OF SIALO PROTEINS ON THE SURFACE OF CULTURED LYMPHOMA CELLS

AUTHOR: MACA R D; HAKES A

JOURNAL: Biochemical and Biophysical Research Communications 74 (4): p
1660-1666 1977
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Unspecified

...ABSTRACT: cultured human Burkitt lymphoma cells (Raji). Cells made deficient in SSA by neuraminidase treatment were incubated for 18 h in medium containing CMP, a potent *inhibitor* of surface sialyl transferase activity. In these cultures, the amount of regenerated SSA was not significantly less than for controls, even though the surface sialyl transferase activity on these cells was *inhibited* by an average of 95%. Emetine, an *inhibitor* of protein synthesis, effectively *inhibited* SSA regeneration. These results support the concept that surface sialoproteins are largely, if not entirely, synthesized intracellularly instead of being assembled on the cell surface...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/14 (Item 14 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002118831 BIOSIS NO.: 197763039687

STUDIES ON THE BIOSYNTHESIS OF GLYCO SPHINGO LIPIDS IN CULTURED MOUSE NEUROBLASTOMA CELLS CHARACTERIZATION AND ACCEPTOR SPECIFICITIES OF N ACETYLGALACTOSAMINYL TRANSFERASES EC-2.4.1.-

AUTHOR: KEMP S F; STOOLMILLER A C

JOURNAL: Journal of Neurochemistry 27 (3): p723-732 1976

ISSN: 0022-3042

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Unspecified

...ABSTRACT: preparations catalyzed the transfer of NeuNAc from CMP-NeuNAc to lactosylceramide (GL-2a), to form GM3. Asialo-GM2 was neither an acceptor nor a competitive *inhibitor* of the sialyltransferase (CMP-NeuNAc: GL-2a N-acetylneuraminyltransferase, EC 2.4.99.-) under a variety of experimental conditions. Enzyme preparations also contained an N...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...*SIALYL TRANSFERASE*

5/3,K/15 (Item 15 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002110340 BIOSIS NO.: 197763031196

SIALIC-ACID UPTAKE BY FIBROBLASTS

AUTHOR: HIRSCHBERG C B; GOODMAN S R; GREEN C

JOURNAL: Biochemistry 15 (16): p3591-3599 1976

ISSN: 0006-2960

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Unspecified

...ABSTRACT: 3H]sialic acid resulted in only 20-40% of the radioactivity within the cells being membrane bound, and 70-90% of this incorporation could be *inhibited* by the addition of 10 mM azide to the incubation medium. The possibility that a small fraction of the total incorporation of sialic acid by...

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*

5/3,K/16 (Item 16 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0002009856 BIOSIS NO.: 197713035848

EFFECT OF PLATELET *INHIBITORS* ON PLATELET SURFACE SIALYL TRANSFERASE ACTIVITY

AUTHOR: WU K K; KU C S L

JOURNAL: Federation Proceedings 36 (3): p380 1977

ISSN: 0014-9446

DOCUMENT TYPE: Article

RECORD TYPE: Citation

LANGUAGE: Unspecified

EFFECT OF PLATELET *INHIBITORS* ON PLATELET SURFACE SIALYL TRANSFERASE ACTIVITY

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/17 (Item 17 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0001379386 BIOSIS NO.: 197457025241

THE SIALIC ACIDS PART 16 ISOLATION OF A MUCIN SIALYL TRANSFERASE FROM SHEEP SUBMAXILLARY GLAND

AUTHOR: CARLSON D M; MCGUIRE E J; JOURDIAN G W; ROSEMAN S

JOURNAL: Journal of Biological Chemistry 248 (16): p5763-5773 1973

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Citation

LANGUAGE: Unspecified

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS: PIG COW FETUIN ERYTHROCYTE HEM AGGLUTINATION *INHIBITOR* PER IODATE OXIDATION

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0001289128 BIOSIS NO.: 197410035283

***INHIBITION* OF SIALYL TRANSFERASE ACTIVITY OF CULTURED HUMAN LYMPHOID CELLS BY CYCLIC AMP**

AUTHOR: KILTON L J; MACA R D; LEWIS L J; BEDELL G N

JOURNAL: Federation Proceedings 33 (3 PART 1): p265 1974
ISSN: 0014-9446
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: Unspecified

***INHIBITION* OF SIALYL TRANSFERASE ACTIVITY OF CULTURED HUMAN LYMPHOID CELLS BY CYCLIC AMP**

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*...

5/3,K/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0000982051 BIOSIS NO.: 197254038565

A NATURAL *INHIBITOR* OF SIALYL TRANSFERASE AND ITS POSSIBLE INFLUENCE ON THIS ENZYME ACTIVITY DURING BRAIN DEVELOPMENT

AUTHOR: DUFFARD R O; CAPUTTO R

JOURNAL: Biochemistry 11 (8): p1396-1400 1972

ISSN: 0006-2960

DOCUMENT TYPE: Article

RECORD TYPE: Citation

LANGUAGE: Unspecified

A NATURAL *INHIBITOR* OF SIALYL TRANSFERASE AND ITS POSSIBLE INFLUENCE ON THIS ENZYME ACTIVITY DURING BRAIN DEVELOPMENT

...REGISTRY NUMBERS: *SIALYL TRANSFERASE*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: *SIALYL TRANSFERASE*

5/3,K/20 (Item 1 from file: 266)

DIALOG(R)File 266:FEDRIP

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00519567

IDENTIFYING NO.: 0182717 AGENCY CODE: AGRIC

MOLECULAR BASIS OF LOS PHASE VARIATION AND SIALYLATION IN HAEMOPHILUS mice

ASSOCIATE INVESTIGATORS: Inzana, T. J.

PERFORMING ORG.: VIRGINIA POLYTECHNIC INSTITUTE, College Of Vet Medicine
, BLACKSBURG, VIRGINIA 24061

...SUMMARY: to other bacterial gale genes. We have confirmed that H. somnus attaches sialic

acid to the terminal galactose of its LOS, and that this sialylation *inhibits* antibody binding to other cell components and enhances resistance to bacterial killing by serum. LOS sialylation by H. somnus is by a mechanism similar to...

DESCRIPTORS: beef cattle; immunology; molecular biology; animal diseases; bacterial diseases (animals); bacteriology; haemophilus somnus; *sialyl transferase*; bacterial genetics; gene cloning; animal pathogens; biosynthesis; lipooligosaccharides; mutants; virulence; homologous chromosomes; dna sequences; polymerase chain reaction; genetic engineering; gene function; bioassays; mice

? s 2 deoxy glucose

S6 385 2 DEOXY GLUCOSE

? s s6 and inhibit? and transferase?

Processing

Processed 10 of 40 files ...

Processing

Processed 30 of 40 files ...

Completed processing all files

385 S6

8640349 INHIBIT?

607127 TRANSFERASE?

S7 2 S6 AND INHIBIT? AND TRANSFERASE?

? rd

>>>Duplicate detection is not supported for File 393.

>>>Records from unsupported files will be retained in the RD set.

S8 2 RD (unique items)

? show files;ds;t/3,k/all

File 5:Biosis Previews(R) 1969-2006/Feb W4

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(c) 2006 Elsevier Eng. Info. Inc.

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(c) 2006 CSA.

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File 136:BioEngineering Abstracts 1966-2006/Jan

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(c) 2006 The HW Wilson Co

File 144:Pascal 1973-2006/Feb W1

(c) 2006 INIST/CNRS

File 155:MEDLINE(R) 1951-2006/Feb 28

(c) format only 2006 Dialog

File 172:EMBASE Alert 2006/Mar 01

(c) 2006 Elsevier Science B.V.

File 266:FEDRIP 2005/Dec

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File 315:ChemEng & Biotech Abs 1970-2005/Dec

(c) 2005 DECHEMA

File 357:Derwent Biotech Res. 1982-2006/Feb W4

(c) 2006 Thomson Derwent & ISI

File 358:Current BioTech Abs 1983-2005/Dec

(c) 2005 DECHEMA

File 369:New Scientist 1994-2006/Aug W4

(c) 2006 Reed Business Information Ltd.

File 370:Science 1996-1999/Jul W3
 (c) 1999 AAAS
 File 399:CA SEARCH(R) 1967-2006/UD=14410
 (c) 2006 American Chemical Society
 File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
 (c) 1998 Inst for Sci Info
 File 40:Enviroline(R) 1975-2005/Dec
 File 41:Pollution Abstracts 1966-2006/Jan
 (c) 2006 CSA.
 File 50:CAB Abstracts 1972-2005/Dec
 (c) 2006 CAB International
 File 103:Energy SciTec 1974-2006/Jan B2
 (c) 2006 Contains copyrighted material
 File 156:ToxFile 1965-2005/Dec W4
 (c) format only 2006 Dialog
 File 162:Global Health 1983-2006/Jan
 (c) 2006 CAB International
 File 305:Analytical Abstracts 1980-2006/Feb W4
 (c) 2006 Royal Soc Chemistry
 File 393:Beilstein Abstracts 2005/Q3
 (c) Beilstein GmbH
 File 35:Dissertation Abs Online 1861-2006/Feb
 (c) 2006 ProQuest Info&Learning
 File 91:MANTIS(TM) 1880-2006/Feb
 2006 (c) Action Potential
 File 149:TGG Health&Wellness DB(SM) 1976-2006/Feb W2
 (c) 2006 The Gale Group
 File 159:Cancerlit 1975-2002/Oct
 (c) format only 2002 Dialog
 File 164:Allied & Complementary Medicine 1984-2006/Mar
 (c) 2006 BLHCIS
 File 444:New England Journal of Med. 1985-2006/Feb W2
 (c) 2006 Mass. Med. Soc.
 File 467:ExtraMED(tm) 2000/Dec
 (c) 2001 Informania Ltd.

Set	Items	Description
S1	0	(SIALYL ADJ TRANSFERASE) (S) INHIBIT?
S2	0	(SIALYL TRANSFERASE) (S) INHIBIT?
S3	0	(SIALIC ACID TRANSFERASE) AND INHIBIT?
S4	21	(SIALYL TRANSFERASE) AND INHIBIT?
S5	20	RD (unique items)
S6	385	2 DEOXY GLUCOSE
S7	2	S6 AND INHIBIT? AND TRANSFERASE?
S8	2	RD (unique items)

>>>KWIC option is not available in file(s): 399

8/3,K/1 (Item 1 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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0002383337 BIOSIS NO.: 197865044324

DE-NOVO ALANINE SYNTHESIS IN ISOLATED OXYGEN DEPRIVED RABBIT MYO CARDIUM
 AUTHOR: TAEGTMEYER H (Reprint); PETERSON M B; RAGAVAN V V; FERGUSON A G;
 LESCH M

AUTHOR ADDRESS: CARBIOVASC DIV, DEP MED, PETER BENT BRIGHAM HOSP, BOSTON
 MASS 02115, USA**USA

JOURNAL: Journal of Biological Chemistry 252 (14): p5010-5018 1977

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: acid (0.5 mM) or leucine (0.5 mM) to the medium did not influence net production of alanine in oxygenated or anoxic papillary muscles. *Inhibitors* of the glycolytic pathway (2-deoxyglucose, iodoacetate, NaF) caused a decline in alanine production by approximately 50%. Alanine production was not affected by variation in media pH. De novo alanine synthesis was significantly reduced when the enzyme alanine aminotransferase was *inhibited* by L-cycloserine, while the *inhibitor* aminooxyacetic acid totally abolished alanine production by hypoxic muscles. Apparently increased alanine production in isolated right ventricular papillary muscles reflects de novo synthesis, is closely...
...REGISTRY NUMBERS: *2 DEOXY GLUCOSE*...

...ALANINE AMINO *TRANSFERASE*
DESCRIPTORS: PYRUVATE 2 DEOXY GLUCOSE IODO ACETATE SODIUM FLUORIDE L CYCLO SERINE METAB-DRUGS GLYCOLYTIC PATHWAY ALANINE AMINO *TRANSFERASE*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*2 DEOXY GLUCOSE*...

...ALANINE AMINO *TRANSFERASE*

8/3,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2006 BIOSIS. All rts. reserv.

0001782464 BIOSIS NO.: 197612048603
INHIBITION OF THE ADAPTATION OF ESCHERICHIA-COLI TO GLYCEROL BY 2 DEOXY GLUCOSE AND 2 DEOXY GLUCOSE 6 PHOSPHATE
AUTHOR: DIETZ G W JR
JOURNAL: Federation Proceedings 35 (7): p1580 1976
ISSN: 0014-9446
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: Unspecified

DESCRIPTORS: ABSTRACT MUTANT HEXOSE PHOSPHATE TRANSPORT SYSTEM PHOSPHO
TRANSFERASE

File 5: Biosis Previews(R) 1969-2006/Feb W4
(c) 2006 BIOSIS

File 6: NTIS 1964-2006/Feb W2
(c) 2006 NTIS, Intl Cpyrght All Rights Res

File 24: CSA Life Sciences Abstracts 1966-2006/Jan
(c) 2006 CSA.

File 34: SciSearch(R) Cited Ref Sci 1990-2006/Feb W3
(c) 2006 Inst for Sci Info

File 40: Enviroline(R) 1975-2005/Dec

File 41: Pollution Abstracts 1966-2006/Jan
(c) 2006 CSA.

File 50: CAB Abstracts 1972-2005/Dec
(c) 2006 CAB International

File 65: Inside Conferences 1993-2006/Mar 01
(c) 2006 BLDSC all rts. reserv.

File 71: ELSEVIER BIOBASE 1994-2006/Feb W4
(c) 2006 Elsevier Science B.V.

File 73: EMBASE 1974-2006/Mar 01
(c) 2006 Elsevier Science B.V.

File 94: JICST-EPlus 1985-2006/Dec W1
(c) 2006 Japan Science and Tech Corp(JST)

File 98: General Sci Abs 1984-2004/Dec
(c) 2005 The HW Wilson Co.

File 103: Energy SciTec 1974-2006/Jan B2
(c) 2006 Contains copyrighted material

***File 103: For access restrictions see Help Restrict.**

File 136: BioEngineering Abstracts 1966-2006/Jan
(c) 2006 CSA.

File 143: Biol. & Agric. Index 1983-2006/Feb
(c) 2006 The HW Wilson Co

File 144: Pascal 1973-2006/Feb W1
(c) 2006 INIST/CNRS

File 155: MEDLINE(R) 1951-2006/Feb 28
(c) format only 2006 Dialog

***File 155: Medline has resumed updating.**

File 156: ToxFile 1965-2005/Dec W4
(c) format only 2006 Dialog

***File 156: ToxFile has resumed updating with UD20051205.**

File 162: Global Health 1983-2006/Jan
(c) 2006 CAB International

File 172: EMBASE Alert 2006/Mar 01
(c) 2006 Elsevier Science B.V.

File 305: Analytical Abstracts 1980-2006/Feb W4
(c) 2006 Royal Soc Chemistry

***File 305: Alert feature enhanced for multiple files, duplicate removal, customized scheduling. See HELP ALERT.**

File 369: New Scientist 1994-2006/Aug W4
(c) 2006 Reed Business Information Ltd.

File 370: Science 1996-1999/Jul W3
(c) 1999 AAAS

***File 370: This file is closed (no updates). Use File 47 for more current information.**

File 393: Beilstein Abstracts 2005/Q3
(c) Beilstein GmbH

File 399: CA SEARCH(R) 1967-2006/UD=14410
(c) 2006 American Chemical Society

***File 399: Use is subject to the terms of your user/customer agreement.**

IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

File 434: SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 1998 Inst for Sci Info

File 35: Dissertation Abs Online 1861-2006/Feb

(c) 2006 ProQuest Info&Learning
 File 91:MANTIS(TM) 1880-2006/Feb
 2006 (c) Action Potential
 File 135:NewsRx Weekly Reports 1995-2006/Feb W3
 (c) 2006 NewsRx
***File 135: Please see HELP NEWS135 for information on select journal titles.**
 File 149:TGG Health&Wellness DB(SM) 1976-2006/Feb W2
 (c) 2006 The Gale Group
 File 159:Cancerlit 1975-2002/Oct
 (c) format only 2002 Dialog
***File 159: Cancerlit is no longer updating.**
 Please see HELP NEWS159.
 File 164:Allied & Complementary Medicine 1984-2006/Mar
 (c) 2006 BLHCIS
 File 266:FEDRIP 2005/Dec
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 (c) 2006 Mass. Med. Soc.
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 (c) 2001 Informania Ltd.
***File 467: F467 will close on February 1, 2006.**

7.

Set	Items	Description
?	s	tunicamycin and treat?
Processing		
Processed	10 of 35 files	...
Processing		
Processed	20 of 35 files	...
Completed processing all files		
	19511	TUNICAMYCIN
	16309178	TREAT?
S1	8209	TUNICAMYCIN AND TREAT?
?	s	s1 and inhibit? and transferase?
Processing		
Processed	10 of 35 files	...
Completed processing all files		
	8209	S1
	8472337	INHIBIT?
	589057	TRANSFERASE?
S2	142	S1 AND INHIBIT? AND TRANSFERASE?
?	rd	
>>>Duplicate detection is not supported for File 393.		
>>>Records from unsupported files will be retained in the RD set.		
S3	79	RD (unique items)
?	s	s3 and (in vivo)
	79	S3
	83390	IN VIVO
S4	0	S3 AND (IN VIVO)
?	s	s3 and (animal? or organism or mouse or human?)
>>>File 5 processing for HUMAN? stopped at HUMAN ANTIHYPERTENSIVE-DRUG		
HYPOKALEMIC ALKALO		
Processing		
Processing		
Processing		
Processing		
Processed	10 of 35 files	...
Processing		

Processing
Processed 20 of 35 files ...
Processing
Completed processing all files
79 S3
26937805 ANIMAL?
647632 ORGANISM
3301469 MOUSE
36473435 HUMAN?
S5 47 S3 AND (ANIMAL? OR ORGANISM OR MOUSE OR HUMAN?)
? rd

>>>Duplicate detection is not supported for File 393.

>>>Records from unsupported files will be retained in the RD set.

S6 47 RD (unique items)
? show files;ds;t/3,k/all
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File 34:SciSearch(R) Cited Ref Sci 1990-2006/Feb W3
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File 103:Energy SciTec 1974-2006/Jan B2
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(c) 2006 CSA.
File 143:Biol. & Agric. Index 1983-2006/Feb
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File 144:Pascal 1973-2006/Feb W1
(c) 2006 INIST/CNRS
File 155:MEDLINE(R) 1951-2006/Feb 28
(c) format only 2006 Dialog
File 156:ToxFile 1965-2005/Dec W4
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File 162:Global Health 1983-2006/Jan
(c) 2006 CAB International
File 172:EMBASE Alert 2006/Mar 01
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File 305:Analytical Abstracts 1980-2006/Feb W4
(c) 2006 Royal Soc Chemistry
File 369:New Scientist 1994-2006/Aug W4
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File 370:Science 1996-1999/Jul W3

(c) 1999 AAAS
 File 393:Beilstein Abstracts 2005/Q3
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 File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
 (c) 1998 Inst for Sci Info
 File 35:Dissertation Abs Online 1861-2006/Feb
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 File 91:MANTIS(TM) 1880-2006/Feb
 2006 (c) Action Potential
 File 135:NewsRx Weekly Reports 1995-2006/Feb W3
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 File 149:TGG Health&Wellness DB(SM) 1976-2006/Feb W2
 (c) 2006 The Gale Group
 File 159:Cancerlit 1975-2002/Oct
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 File 266:FEDRIP 2005/Dec
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Set	Items	Description
S1	8209	TUNICAMYCIN AND TREAT?
S2	142	S1 AND INHIBIT? AND TRANSFERASE?
S3	79	RD (unique items)
S4	0	S3 AND (IN VIVO)
S5	47	S3 AND (ANIMAL? OR ORGANISM OR MOUSE OR HUMAN?)
S6	47	RD (unique items)

>>>KWIC option is not available in file(s): 399

6/3,K/1 (Item 1 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
 (c) 2006 BIOSIS. All rts. reserv.

0015491312 BIOSIS NO.: 200510185812
***Inhibition* of lipid-linked oligosaccharide (LLO) arrests capillary endothelial cells in G1 and induces apoptosis**
 AUTHOR: Banerjee Dipak K (Reprint); Martinez Juan A; Bakshi Krishna
 AUTHOR ADDRESS: Univ Puerto Rico, Sch Med, Dept Biochem, San Juan, PR 00936 USA**USA
 JOURNAL: FASEB Journal 18 (8, Suppl. S): pC153-C154 MAY 14 2004 2004
 CONFERENCE/MEETING: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology Boston, MA, USA June 12 -16, 2004; 20040612
 SPONSOR: Amer Soc BioChem & Mol Biol
 Int Union Biochem & Mol Biol
 ISSN: 0892-6638
 DOCUMENT TYPE: Meeting; Meeting Abstract
 RECORD TYPE: Abstract
 LANGUAGE: English

***Inhibition* of lipid-linked oligosaccharide (LLO) arrests capillary endothelial cells in G1 and induces apoptosis**
 ...ABSTRACT: G1NAC(2)-PP-Dolichol (lipid-linked oligosaccharide, LLO). Defect in the protein N-glycosylation machinery has been found to be

responsible for pathophysiology of many *human* diseases including the Congenital Defect in Glycoprotein Syndrome (CDGS). We have been studying the regulation of LLO biosynthesis and its ramification to angiogenesis [Banerjee, DK...

...development, and is considered a 'key step' in tumor growth and invasion. The cellular and molecular events leading to angiogenesis are a multi-step process. *Treatment* of CE with *tunicamycin* (a glucosamine-containing pyrimidine nucleoside and an *inhibitor* of N-acetylglucosamine I-phosphate *transferase*), down-regulated the cell growth, LLO biosynthesis and the expression of cell surface N-glycans. The response was time- and concentration-dependent, and could not be reversed by a protein synthesis *inhibitor* or by fibroblast growth factor-2 (FGF-2). Increased expression of Bip/GRP-78 and GRP-94 (ER chaperons) indicated "ER stress". Reduced expression of...

...REGISTRY NUMBERS: *tunicamycin*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...N-acetylglucosamine 1 phosphate
transferase; *tunicamycin*--

6/3,K/2 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0013539789 BIOSIS NO.: 200200133300

Expression of bisecting N-acetylglucosaminyltransferase-III in *human* hepatocarcinoma tissues, fetal liver tissues, and hepatoma cell lines of Hep3B and HepG2

AUTHOR: Song Eun-Young; Kang Sung-Koo; Lee Young-Choon; Park Young-Guk; Chung Tae-Hwa; Kwon Do-Hwan; Byun Si-Myung; Kim Cheorl-Ho (Reprint)

AUTHOR ADDRESS: Department of Biochemistry and Molecular Biology, College of Oriental Medicine, Dongguk University, Sukjang-Dong 707, Kyungju, 780-714, South Korea**South Korea

JOURNAL: Cancer Investigation 19 (8): p799-807 November, 2001 2001

MEDIUM: print

ISSN: 0735-7907

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

Expression of bisecting N-acetylglucosaminyltransferase-III in *human* hepatocarcinoma tissues, fetal liver tissues, and hepatoma cell lines of Hep3B and HepG2

ABSTRACT: In this paper, uridine diphosphate

(UDP)-N-acetylglucosamine/beta-D-mannoside beta-1,4

N-acetylglucosaminyltransferase III (GlcNAc-*transferase*-III C

2.4.1.144) activity was determined in *human* hepatoma cell lines of Hep3B and HepG2, and also compared with those of normal liver tissues and primary hepatocytes. GlcNAc-*transferase*-III enzymes of Hep3B and HepG2 were mainly detected in the membrane fraction. When GlcN, GlcN-biant-PA and UDP-GlcNAc were used as substrates, the Km values (4.7 mM for UDP-GlcNAc and 1.1 mM for GlcN, GlcN-biant-PA) of Hep3B GlcNAc-*transferase*-III were distinguishable from those of HepG2 GlcNAc-*transferase*-III (6.8 mM for UDP-GlcNAc and 3.4 mM for GlcN, GlcN-biant-PA). Furthermore, Hep3B enzyme in membrane fraction showed about 1...

...mg) than that of HepG2 (1066 pmol/hr/mg). Normal liver cells and primary adult hepatocytes are characterized by a very low level of GlcNAc-

transferase-III activity, whereas *human* hepatoma cells exhibited high activities. These data were supported by reverse transcription-polymerase chain reaction results, showing that expression of the GlcNAc-*transferase*-III mRNA increased in proportion to the enzymatic activities. Although the mechanism underlying the induction of this enzyme is unknown, lectin blot analysis showed that oligosaccharides in many glycoproteins were observed in hepatoma cells. By *treating* hepatocarcinoma cultures that express GlcNAc-*transferase*-III with *inhibitors* (*tunicamycin*, deoxymannojirimycin, and swainsonine) of different steps of the glycosylation, we provide evidence that expression of GlcNAc-*transferase*-III mRNA is dependent on glycosylation of cellular proteins.

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Primates, Mammalia, Vertebrata, Chordata,
Animalia

...ORGANISMS: *human* hepatoma cells...

...*human* hepatoma cells...

...*human* (Hominidae

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: ...activity, expression, *inhibition*

6/3,K/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0011943934 BIOSIS NO.: 199900203594

Regulation of UDP-N-acetylglucosamine:dolichyl-phosphate

N-acetylglucosamine-1-phosphate *transferase* by retinoic acid in P19 cells

AUTHOR: Meissner Joachim D; Naumann Andreas; Mueller Walter H; Scheibe Renate J (Reprint)

AUTHOR ADDRESS: Zentrum Physiologie, Medizinische Hochschule Hannover, 30623, Hannover, Germany**Germany

JOURNAL: Biochemical Journal 338 (2): p561-568 March 1, 1999 1999

MEDIUM: print

ISSN: 0264-6021

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

Regulation of UDP-N-acetylglucosamine:dolichyl-phosphate

N-acetylglucosamine-1-phosphate *transferase* by retinoic acid in P19 cells

ABSTRACT: UDP-N-acetylglucosamine:dolichyl-phosphate

N-acetylglucosamine-1-phosphate *transferase* (GPT) is the first enzyme in the dolichol pathway of protein N-glycosylation, and is implicated in the developmental programmes of a variety of eukaryotes...

...of all-trans-retinoic acid (RA) on the levels of GPT protein and enzymic activity, and on the transcription rate of the GPT gene, in *mouse* P19 teratocarcinoma cells. RA caused a dose-dependent and protein-synthesis-dependent induction of enzyme activity. The maximum induction of GPT activity (about 3-fold...

...of incorporation of (3H)mannose into Glc3Man9GlcNAc2. Enzymic activities paralleled GPT gene expression. The GPT gene was induced (2-fold) after 7 h of RA *treatment*. An approx. 3-fold increase in a 48 kDa GPT protein

and approx. 4-fold increases in the levels of three GPT transcripts (1.8, 2.0 and 2.2 kb) were observed after 2 days of RA *treatment*. The enhanced levels of GPT protein and mRNAs began to decline 3 days after the initiation of differentiation, and GPT expression was down-regulated during...

...level in differentiated P19 cells. The results indicate that the RA-induced enzyme activity was mainly determined by increased transcription of the GPT gene. RA-*treated* P19 cells were about 4-fold more resistant to *tunicamycin*, a fungal antibiotic which *inhibits* GPT, than were control cells. In addition, GPT activity in membranes from RA-*treated* P19 cells exhibited approx. 4-fold increased resistance to *tunicamycin* compared with activity in membranes from untreated control cells, demonstrating that resistance to *tunicamycin* is correlated with induced GPT activity. Furthermore, increased GPT activity had regulatory significance with regard to the rate of incorporation of (3H)mannose into Glc3Man9GlcNAc2...

...ENZYME COMMISSION NUMBER: UDP-N-acetylglucosamine:dolichyl-phosphate
N-acetylglucosamine-1-phosphate *transferase*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Rodentia, Mammalia, Vertebrata, Chordata,
Animalia

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: ...UDP-N-acetylglucosamine:dolichyl-phosphate
N-acetylglucosamine-1-phosphate *transferase*--...

...*mouse* GPT gene {*mouse* UDP-N-acetylglucosamine:dolichyl-phosphate
N-acetylglucosamine-1-phosphate *transferase* gene

6/3,K/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0011438582 BIOSIS NO.: 199800232829

**Activity of N-acetylglucosamine-1-phosphate *transferase* in sheep liver
microsomes: In vivo and in vitro *inhibition* by *tunicamycin***

AUTHOR: Stewart P L (Reprint)

AUTHOR ADDRESS: CSIRO Australian Anim. Health Lab., Private Bag 24,
Geelong, VIC 3220, Australia**Australia

JOURNAL: Research in Veterinary Science 64(1): p31-35 Jan.-Feb., 1998
1998

MEDIUM: print

ISSN: 0034-5288

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**Activity of N-acetylglucosamine-1-phosphate *transferase* in sheep liver
microsomes: In vivo and in vitro *inhibition* by *tunicamycin***

...ABSTRACT: of livestock known as annual ryegrass toxicity, caused by ingestion of bacteria) toxins called corynetoxins, has been shown to be produced experimentally by injection of *tunicamycin*, a related antibiotic. In this study the effects of *tunicamycin* *inhibition* on the activity of the enzyme, N-acetylglucosamine-1-phosphate *transferase*, in sheep liver rough microsomes were measured in vitro and in vivo. Enzyme activity was dependent on Triton X-100 and exogenous dolichol phosphate for maximal activity, although there was measurable activity in their absence. The *transferase* enzyme was very sensitive to in vitro (*inhibition* can be detected below 10 ng ml⁻¹). In vivo, sheep *treated*

parenterally with a single dose of *tunicamycin* showed a time and dose-dependent decrease in enzyme activity, which was almost completely *inhibited* for up to 14 days after a sublethal dose of toxin. In addition, the yield of rough microsomes was lower from toxin-*treated* sheep than from control *animals*.

...REGISTRY NUMBERS: *tunicamycin*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Artiodactyla, Mammalia, Vertebrata, Chordata, *Animalia*

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *tunicamycin*--...

...antiinfective-drug, *inhibition*; ...

...N-acetylglucosamine-1-phosphate *transferase*

6/3,K/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0011288418 BIOSIS NO.: 199800082665
Enhanced stimulatory adenylyl cyclase signaling during opioid dependence is associated with a reduction in palmitoylated GSalpha
AUTHOR: Ammer Hermann (Reprint); Schulz Ruediger
AUTHOR ADDRESS: Inst. Pharmacol. Toxicol. and Pharmacy, Univ. Munich, Koeniginstrasse 16, 80539 Muenchen, Germany**Germany
JOURNAL: Molecular Pharmacology 52 (6): p993-999 Dec., 1997 1997
MEDIUM: print
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic opioid *treatment* of stably mu-opioid receptor transfected *human* mammary epidermoid A431 carcinoma cells (clone A431/mu13) results in sensitization of adenylyl cyclase (AC), a cellular adaptation associated with drug dependence. Up-regulation of...

...in the quantity of stimulatory G proteins and the maximum catalytic activity of AC. Here, we report that detergent extracts from membranes of chronically morphine-*treated* (10 muM; 2 days) A431/mu13 cells display higher stimulatory AC activities as assessed in the S49cyc-reconstitution assay. This finding is most likely due...

...subunits, which per se stimulate AC in S49cyc- membranes, failed to affect the difference in reconstitutive AC activity. Moreover, both chemical depalmitoylation by hydroxylamine and *inhibition* of palmitoyl-CoA *transferase* in vivo by *tunicamycin* *treatment* increased the reconstitutive activity of detergent extracts and eliminated the differences between native and opioid-dependent cells, indicating that the increase in stimulatory activity is due to depalmitoylation of Gsalph. Indeed, metabolic labeling studies with (3H)palmitic acid revealed that chronic opioid *treatment* reduces considerably the fraction of palmitoylated Gsalph in the plasma membrane. Furthermore, high affinity (3H)forskolin binding experiments demonstrated that depalmitoylated Gsalph is able to...

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Primates, Mammalia, Vertebrata, Chordata, *Animalia*

COMMON TAXONOMIC TERMS: *Animals*;

6/3,K/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0008219178 BIOSIS NO.: 199293062069
**FUNCTIONAL AND MORPHOLOGICAL CHANGES INDUCED BY *TUNICAMYCIN* IN DIVIDING
AND CONFLUENT ENDOTHELIAL CELLS**
AUTHOR: TIGANIS T (Reprint); LEAVER D D; HAM K; FRIEDHUBER A; STEWART P;
DZIADEK M
AUTHOR ADDRESS: DEP PHARMACOL, UNIV MELBOURNE, PARKVILLE, VICTORIA 3052,
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JOURNAL: Experimental Cell Research 198 (2): p191-200 1992
ISSN: 0014-4827
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

**FUNCTIONAL AND MORPHOLOGICAL CHANGES INDUCED BY *TUNICAMYCIN* IN DIVIDING
AND CONFLUENT ENDOTHELIAL CELLS**

ABSTRACT: Cultured bovine aortic endothelial cells *treated* with
tunicamycin, an *inhibitor* of glycoprotein synthesis, developed a
concentration-dependent *inhibition* of N-acetylglucosamine-1-phosphate
transferase activity, and this *inhibition* was correlated with a
substantial decrease in [3H]mannose incorporation by the cells.
Endothelial cells were very sensitive to *tunicamycin*, and changes in
their morphology occurred as a result of the *inhibition* of glycoprotein
synthesis. The cells became elongated, the surface irregular, roughened,
and granular, and there was an increase in the interstitial space between
the cells...

...modified. These morphological changes coincided with functional
impairment with the permeability of endothelial cell monolayers to both
125I-albumin and [3H]inulin being increased by *treatment* with
tunicamycin (10⁻⁶ M) for 24 h. These results indicate that the
synthesis of glycoproteins is crucial for cell-cell adhesion and the
functional properties of...

...REGISTRY NUMBERS: *TUNICAMYCIN*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Artiodactyla, Mammalia, Vertebrata, Chordata,
Animalia

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*

6/3,K/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0005704943 BIOSIS NO.: 198784059092
**BIOLOGICAL AND BIOCHEMICAL CHARACTERIZATION OF *TUNICAMYCIN*-RESISTANT
LEISHMANIA-MEXICANA MECHANISM OF DRUG RESISTANCE AND VIRULENCE**
AUTHOR: KINK J A (Reprint); CHANG K-P
AUTHOR ADDRESS: DEP MICROBIOL IMMUNOL, UNIV HEALTH SCI/CHICAGO MED SCH,
CHICAGO, ILL 60664, USA**USA
JOURNAL: Infection and Immunity 55 (7): p1692-1700 1987
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: ENGLISH

1BIOLOGICAL AND BIOCHEMICAL CHARACTERIZATION OF *TUNICAMYCIN*-RESISTANT
LEISHMANIA-MEXICANA MECHANISM OF DRUG RESISTANCE AND VIRULENCE

ABSTRACT: A parasitic protozoan, *Leishmania mexicana amazonensis*, was previously made resistant to *tunicamycin* (J. A. Kink and K.-P. Chang, Proc. Natl. Acad. Sci. USA 84:1253-1257, 1987). In the present study, six different *tunicamycin*-resistant variants were biologically and biochemically compared with their parental wild type to further delineate the mechanism of *tunicamycin* resistance and that of their virulence observed. In contrast to their parental wild type, all *tunicamycin*-resistant variants were found to grow and differentiate in *tunicamycin*-containing medium. The 50% lethal doses of *tunicamycin* for variants resistant to 10 or 80 .mu.g of *tunicamycin* per ml were 20- and 100-fold higher, respectively, than that of the wild type. Specific activity of the microsomal N-acetylglucosamine-1-phosphate *transferase* was 4- to 12-fold higher in the *tunicamycin*-resistant cells than in their parental wild type and *tunicamycin*-sensitive revertants. The level of the enzyme activity is proportional to the degree of drug resistance. *Inhibition* kinetics studies showed that the enzyme from all groups was equally sensitive to the drug, with a 50% effective concentration of 1 to 1.3 .mu.g of *tunicamycin* per ml. Thus, *tunicamycin* resistance of the variants is caused primarily by an increased level of their enzyme without alteration of its structure. Protein glycosylation determined by the incorporation of 2-D-[3H]mannose was about twofold higher in the *tunicamycin*-resistant variants than in their parental wild type. The increased glycosyltransferase activity in the latter apparently renders their protein glycosylation insensitive to the *inhibition* by *tunicamycin*. A major membrane glycoprotein of 63 kilodaltons (gp63) on the leishmania surface was found to be about threefold higher in the *tunicamycin*-resistant variants than in the wild type, as determined by immunoprecipitation with a monoclonal antibody specific for this antigen. *Tunicamycin* *treatment* of the wild type and *tunicamycin*-resistant variants caused changes in the electrophoretic mobility of this molecule, indicating a higher degree of its glycosylation in the latter cells. The *tunicamycin*-resistant variants parasitized macrophages in vitro more effectively than did the wild type, accounting for their virulence seen in mice. Thus, a high level of the glycosyltransferase enables the *tunicamycin*-resistant cells not only to overcome the *inhibitory* effect of *tunicamycin* on protein glycosylation but also to express their virulence, possibly by regulating N glycosylation of leishmanial proteins critical for leishmanias to establish intracellular parasitism.

...REGISTRY NUMBERS: *TUNICAMYCIN*

DESCRIPTORS: LEISHMANIA-MEXICANA-AMAZONENSIS *MOUSE* MICROSOMAL N
ACETYLGLUCOSAMINE-1-PHOSPHATE *TRANSFERASE* LEVEL PROTEIN GLYCOSYLATION
MAJOR MEMBRANE GLYCOPROTEIN MACROPHAGE PARASITIZATION
DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Protozoa, Invertebrata, *Animalia*; ...

...Rodentia, Mammalia, Vertebrata, Chordata, *Animalia*

...COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*

6/3,K/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0005658434 BIOSIS NO.: 198784012583

MINOR MODIFICATIONS TO THE STRUCTURE OF *TUNICAMYCIN* LEAD TO LOSS OF THE

BIOLOGICAL ACTIVITY OF THE ANTIBIOTIC

AUTHOR: HASHIM O H (Reprint); CUSHLEY W
AUTHOR ADDRESS: DEP BIOCHEM, UNIV GLASGOW, GLASGOW G12 8QQ, UK**UK
JOURNAL: Biochimica et Biophysica Acta 923 (3): p362-370 1987
ISSN: 0006-3002
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

MINOR MODIFICATIONS TO THE STRUCTURE OF *TUNICAMYCIN* LEAD TO LOSS OF THE BIOLOGICAL ACTIVITY OF THE ANTIBIOTIC

ABSTRACT: Three analogues of *tunicamycin*, each with minor alterations in structure in different regions of the molecule, have been employed to study the effects of such modifications upon the biological activity of the antibiotic. The data indicate that any modification of structure results in loss of the ability of the antibiotic to *inhibit* N-glycosylation of proteins. In contrast to *tunicamycin* itself, none of the analogues had any deleterious effects upon cellular macromolecule synthesis, nor upon the kinetics of export of de novo synthesized IgM or IgG molecules from *treated* rat hybridoma cells. In addition, the incorporation of tritiated sugars into acid-precipitate macromolecules was not *inhibited*. Endoglycosidase H digestion of isolated IgG molecules further suggested that the analogues employed did not interfere with qualitative glycosylation at the level of N-acetylglucosamine *transferase* I and II in the golgi apparatus. The data are consistent with the interpretation that *tunicamycin* has very precise structural requirements for expression of *inhibitory* effects upon protein glycosylation, and that small variations of structure can lead to loss of its *inhibitory* effects.

...REGISTRY NUMBERS: *TUNICAMYCIN*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Rodentia, Mammalia, Vertebrata, Chordata,
Animalia

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*

6/3,K/9 (Item 9 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0004723107 BIOSIS NO.: 198580032002

N ACETYLGLUCOSAMINYL *TRANSFERASES* FROM THE PUPAL INSTAR OF THE STABLE FLY STOMOXYS-CALCITRANS

AUTHOR: MAYER R T (Reprint); CHEN A C

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JOURNAL: Archives of Insect Biochemistry and Physiology 2 (2): p161-180 1985

ISSN: 0739-4462

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

N ACETYLGLUCOSAMINYL *TRANSFERASES* FROM THE PUPAL INSTAR OF THE STABLE FLY STOMOXYS-CALCITRANS

ABSTRACT: N-acetylglucosaminyl *transferases* from pupae of *S. calcitrans* (L.) were studied in 10,000 g pellet suspensions. Characterization of

these enzymes was based on formation of glycolipids (i.e., Dol.cntdot.PP-GlcNAC [dolichol pyrophosphate.cntdot.N-acetyl glucosamine] and Dol.cntdot.PP-(GlcNAC)2), oligosaccharide lipids and glycoproteins. Studies on *transferase* activity during the pupal instar showed that there were 2 peaks of activity; the 1st peak was on day 0 (prepupae) and the 2nd at 3 days after pupation. Subcellular fractionation indicated that 10,000 g and 100,000 g pellets contained most of the *transferase* activities. The *transferases* required divalent cations (either Mn2+ or Mg2+). The pH optimum, which varied for each of the products formed, was 7.5 for glycolipids, 7.0...

...the amount of Dol.cntdot.PP-GlcNAC and Dol.cntdot.PP.cntdot.(GlcNAC)2 formed, but had little effect on oligosaccharide lipid and glycoprotein formation. *Tunicamycin* was a potent *inhibitor* of glycolipid formation with an I50 of 1.8-4.8 nM. *Tunicamycin* acts by preventing the transfer of GlcNAC-1-P from UDP-GlcNAC to Dol.cntdot.P. UMP reverses glycolipid formation, yielding UDP-GlcNAC. Some characterization of the products was performed. Glycolipids were Dol.cntdot.PP-GlcNAC and Dol.cntdot.PP-(GlcNAC)2. Glycoprotein was rapidly solubilized by protease and detergent *treatments*, whereas oligosaccharide lipids appeared to be acid-labile, pyrophosphate-containing lipids. The apparent kinetic constants for the formation of glycolipids were as follows: UDP-GlcNAC...
...REGISTRY NUMBERS: N-ACETYLGLUCOSAMINYL *TRANSFERASES*; ...

...*TUNICAMYCIN*;

DESCRIPTORS: GLYCOLIPIDS OLIGOSACCHARIDE LIPIDS GLYCOPROTEINS *TUNICAMYCIN*
PROTEASE

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Insecta, Arthropoda, Invertebrata, *Animalia*

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: N-ACETYLGLUCOSAMINYL *TRANSFERASES*;

TUNICAMYCIN;

6/3,K/10 (Item 10 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0004325113 BIOSIS NO.: 198478060520

***TUNICAMYCIN* *INHIBITS* GANGLIOSIDE BIOSYNTHESIS IN RAT LIVER GOLGI
APPARATUS BY BLOCKING SUGAR NUCLEOTIDE TRANSPORT ACROSS THE MEMBRANE
VESICLES**

AUTHOR: YUSUF H K M (Reprint); POHLENTZ G; SANDHOFF K

AUTHOR ADDRESS: INST ORGANISCHE CHEMIE BIOCHEMIE UNIV BONN,

GERHARD-DOMAGK-STR 1, 5300 BONN 1, FRG**WEST GERMANY

JOURNAL: Proceedings of the National Academy of Sciences of the United
States of America 80 (23): p7075-7079 1983

ISSN: 0027-8424

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

***TUNICAMYCIN* *INHIBITS* GANGLIOSIDE BIOSYNTHESIS IN RAT LIVER GOLGI
APPARATUS BY BLOCKING SUGAR NUCLEOTIDE TRANSPORT ACROSS THE MEMBRANE
VESICLES**

...ABSTRACT: ganglioside GM1 in intact rat liver Golgi-derived vesicles is stimulated by phosphatidylglycerol as much (about 20-fold) as by Triton X-100. The antibiotic *tunicamycin* *inhibits* strongly the synthesis, in the presence as well as in the absence of the phospholipid, but has no effect when Golgi membranes are solubilized with detergent. In Pronase-

treated Golgi vesicles, which retain full enzyme activity, both phospholipid dependence and *tunicamycin* *inhibition* of the synthesis disappear completely. When freshly prepared Golgi vesicles are incubated with 125 .mu.M UDP-[3H]Gal for 10 min at 30.degree...

...transported into the vesicles at a rate of .apprx. 85 pmol/mg of protein per min, 92% of which remains firmly bound to the membrane. *Tunicamycin* *inhibits* this transport in a concentration-dependent manner. Carrier proteins probably exist in rat liver Golgi vesicles which mediate the transport of the sugar nucleotide UDP-Gal and that face the cytoplasmic side of the vesicles. Although the mechanism of phosphatidylglycerol-induced stimulation of the synthetic activity remains unclear, *tunicamycin* probably *inhibits* ganglioside biosynthesis by blocking the transport of the nucleotide sugar and not by *inhibiting* the *transferase* directly.

...REGISTRY NUMBERS: *TUNICAMYCIN*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Rodentia, Mammalia, Vertebrata, Chordata,

Animalia

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*

6/3,K/11 (Item 11 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0004172772 BIOSIS NO.: 198477004683

SELECTIVE CYTO TOXICITY OF PURIFIED HOMOLOGUES OF *TUNICAMYCIN* ON TRANSFORMED BALB-3T3 FIBROBLASTS

AUTHOR: SEIBERG M (Reprint); DUKSIN D

AUTHOR ADDRESS: DEP BIOPHYSICS, WEIZMANN INST SCIENCE, REHOVOT 76100, ISRAEL**ISRAEL

JOURNAL: Cancer Research 43 (2): p845-850 1983

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

SELECTIVE CYTO TOXICITY OF PURIFIED HOMOLOGUES OF *TUNICAMYCIN* ON TRANSFORMED BALB-3T3 FIBROBLASTS

ABSTRACT: The selective cytotoxicity of *tunicamycin* homologues against SV40-transformed 3T3 cells (SV40-3T3) [*mouse*] was examined. Incubation of 3T3 or virally transformed 3T3 cells with 4 different homologues (A1, A2, B1 and B2 at 0.1 to 0.25...

...unaffected. Cytotoxicity against nontransformed cells occurred only when higher doses (at least 5-fold) A2-, B1- and B2-tunicamycins were used. In contrast, these homologues *inhibited* proliferation of 3T3 cells, even when doses of 0.5 .mu.g/ml were used. These cytotoxic effects are dose-dependent, and maximal cytotoxicity of each homologue is achieved at a different concentration in each cell type. Apparently, *tunicamycin* homologues have selective cytotoxicity against transformed cells. Incorporation of [3H]mannose into acid-precipitable macromolecules synthesized by transformed cells was strongly *inhibited* (70-75%) by A1- and B2-tunicamycins at 0.01-0.05 .mu.g/ml, while incorporation by 3T3 cells was not affected. At higher concentrations of the above tunicamycins (0.5-1 .mu.g/ml), [3H]mannose incorporation by both 3T3 and SV40-3T3 cells was *inhibited* > 95%. In contrast, the effect of these *tunicamycin* homologues on protein synthesis in 3T3 and SV40-3T3

fibroblasts was less pronounced since the incorporation of amino acids was *inhibited* by .apprx. 20%. Very little *inhibition* of amino acid incorporation occurred when 3T3 or SV40-3T3 cells were *treated* with B2-*tunicamycin*. A1-*tunicamycin* *inhibited* [3H]proline incorporation and slightly increased [3H]tyrosine incorporation into cell layers of 3T3 cells. Examination of secreted proteins synthesized by these cells on sodium dodecyl sulfate:polyacrylamide gel electrophoresis revealed that both 3T3 and SV40-3T3 cells *treated* with homologues produced partially glycosylated macromolecules, such as procollagen and fibronectin, and failed to convert procollagen to collagen. *Tunicamycin* homologues also *inhibited* the N-acetylglucosamine-1-phosphate *transferase* activity found in microsomes prepared from 3T3 and virally transformed 3T3 fibroblasts. Apparently, the cytotoxic activity of purified homologues of *tunicamycin* against transformed fibroblasts might be due to the selective *inhibition* of glycosylation and to the differences in the membrane solubilities of the homologues.

DESCRIPTORS: *MOUSE* SV-40 ANTINEOPLASTIC-DRUG N ACETYL GLUCOSAMINE 1 PHOSPHATE *TRANSFERASE*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Rodentia, Mammalia, Vertebrata, Chordata, *Animalia*

...COMMON TAXONOMIC TERMS: *Animals*;

6/3,K/12 (Item 12 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0003973550 BIOSIS NO.: 198376064985

BIOSYNTHESIS OF MURINE IMMUNO GLOBULIN D HETEROGENEITY OF GLYCOSYLATION

AUTHOR: VASILOV R G (Reprint); PLOEGH H L

AUTHOR ADDRESS: INST GENET, UNIV COLOGNE, WEYERTAL 121, D-5000 COLOGNE 41, W GER**WEST GERMANY

JOURNAL: European Journal of Immunology 12 (10): p804-813 1982

ISSN: 0014-2980

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: degree of heterogeneity in N-linked glycosylation, most likely involving the number of glycan sidechains that are attached. Similar findings have recently been documented for *human* IgD. Further modifications of the oligosaccharide side chains follow the pathways established for numerous other glycoproteins. Under conditions where N-linked glycosylation was *inhibited* by *tunicamycin* (TM), the presence of neuraminidase-sensitive forms of secretory IgD could be shown. Secretory IgD from TM-*treated* cells was susceptible to mild alkaline hydrolysis. The findings argue strongly for the presence of O-linked, sialic acid-carrying sugars on murine IgD. Both...

...sized molecules. Since B1-8..mu. and B1-8..delta. express identical variable regions and L-chains, such differences must be attributed to isotypic differences. *Inhibition* of glycosylation affected neither secretion nor assembly of either IgM or IgD.

...REGISTRY NUMBERS: *TUNICAMYCIN*;

DESCRIPTORS: B-1-8.DELTA CELLS B-1-8.MU CELLS *HUMAN* *TUNICAMYCIN*

NEURAMINIDASE METABOLIC-DRUG H-2K ANTIGEN H-2D ANTIGEN IMMUNO GLOBULIN M GLYCOSYL *TRANSFERASE*

DESCRIPTORS:

...MAJOR CONCEPTS: *Human* Medicine, Medical Sciences

...BIOSYSTEMATIC NAMES: Primates, Mammalia, Vertebrata, Chordata, *Animalia*;

...Rodentia, Mammalia, Vertebrata, Chordata, *Animalia*
...COMMON TAXONOMIC TERMS: *Animals*;
CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*;

6/3,K/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0003897569 BIOSIS NO.: 198375081512
REVERSIBLY PERMEABLE HEPATOMA CELLS IN CULTURE
AUTHOR: BALINSKA M (Reprint); SAMSONOFF W A; GALIVAN J
AUTHOR ADDRESS: CENT LAB, RES, NEW YORK STATE DEP HEALTH, ALBANY, NY 12201,
USA**USA
JOURNAL: Biochimica et Biophysica Acta 721 (3): p253-261 1982
ISSN: 0006-3002
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A brief *treatment* of H35 [rat] hepatoma cells with lysolecithin
resulted in a cell population which is permeable to low-MW charged
molecules that cannot normally cross the...

...support for this view comes from that the fact that the permeable cells
could seal when placed in enriched medium. The process of sealing was
inhibited by cycloheximide and *tunicamycin*. The sealed cells, whose
surfaces appeared identical to those of untreated cells by scanning
electron microscopy, were fully capable of cell division when exposed to
...

...REGISTRY NUMBERS: *TUNICAMYCIN*;
DESCRIPTORS: RAT HEPATOMA H-35 CELLS PLASMA MEMBRANE DEXAMETHASONE
HORMONE-DRUG CYCLO HEXIMIDE *TUNICAMYCIN* METABOLIC-DRUG LACTATE
DEHYDROGENASE EC-1.1.1.27 TYROSINE AMINO *TRANSFERASE* EC-2.6.1.5 SCANNING
ELECTRON MICROSCOPY LYSO LECITHIN DNA THYMIDINE CELLULAR SEALING FOLATE
COENZYME TRANSPORT

DESCRIPTORS:
...BIOSYSTEMATIC NAMES: Rodentia, Mammalia, Vertebrata, Chordata,
Animalia
COMMON TAXONOMIC TERMS: *Animals*;
CHEMICALS & BIOCHEMICALS: ...*TUNICAMYCIN*;

6/3,K/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0003535537 BIOSIS NO.: 198273039464
**EFFECT OF *TUNICAMYCIN* IN EPIDERMAL GLYCO PROTEIN AND GLYCOSAMINO GLYCAN
SYNTHESIS IN-VITRO**
AUTHOR: KING I A (Reprint); TABIOWO A
AUTHOR ADDRESS: MRC UNIT ON THE EXPERIMENTAL PATHOL SKIN, THE MED SCH
BIRMINGHAM B15 2TJ, UK**UK
JOURNAL: Biochemical Journal 198 (2): p331-338 1981
ISSN: 0264-6021
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

EFFECT OF *TUNICAMYCIN* IN EPIDERMAL GLYCO PROTEIN AND GLYCOSAMINO GLYCAN

SYNTHESIS IN-VITRO

ABSTRACT: When pig ear skin slices were cultured for 18 h in the presence of 1 μ g *tunicamycin*/ml the incorporation of D-[3H]glucosamine into the epidermis, solubilized with 8 M urea/5% (wt/vol) sodium dodecyl sulfate, was *inhibited* by 45-55%. This degree of *inhibition* was not increased by using up to 5 μ g *tunicamycin*/ml or by *treating* the skin slices with *tunicamycin* for up to 8 days. Incorporation of (U[uniformly labeled]-14C)-L-amino acids under these conditions was not affected by *tunicamycin*. Polyacrylamide gel electrophoresis indicated that labeling the major glycosaminoglycan peak with D-[3H]glucosamine was unaffected; that of the faster migrating glycoprotein components was decreased in the presence of *tunicamycin*. Subcellular fractionation indicated that *tunicamycin* specifically *inhibited* the incorporation of D-[3H]glucosamine but not (U-14C)-L-amino acids into particulate (mainly plasma membrane) glycoproteins by *apprx.* 70%. Labeling of soluble...

...into all glycoprotein components, indicating that plasma membrane glycoproteins contained mainly N-asparagine-linked oligosaccharides. Cellulose acetate electrophoresis of cellular and extracellular glycosaminoglycans showed that *tunicamycin* had no significant effect on the synthesis of the major component, hyaluronic acid. Incorporation of D-[3H]glucosamine and 35SO42- into sulfated glycosaminoglycans was *inhibited* by *apprx.* 50%. This *inhibition* was partially overcome, at least in the cellular fraction, by 2 mM-p-nitrophenyl β -D-xyloside indicating that *tunicamycin*-*treated* epidermis retained the ability to synthesize sulfated glycosaminoglycan chains. *Tunicamycin* may affect the synthesis and/or degradation of proteoglycan core proteins or xylosyltransferase. EM examination of epidermis *treated* with *tunicamycin* for up to 4 days revealed no significant changes in cell-surface morphology or in epidermal-cell adhesion. N-asparagine-linked carbohydrates played little role...

...REGISTRY NUMBERS: *TUNICAMYCIN*;

DESCRIPTORS: PIG PLASMA MEMBRANE XYLOSYL *TRANSFERASE*

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Artiodactyla, Mammalia, Vertebrata, Chordata, *Animalia*

...COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*;

6/3,K/15 (Item 15 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

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0002488487 BIOSIS NO.: 197968074978

A DOLICHOL LINKED TRI SACCHARIDE FROM CENTRAL NERVOUS TISSUE STRUCTURE AND BIOSYNTHESIS

AUTHOR: WAECHTER C J (Reprint); HARFORD J B

AUTHOR ADDRESS: DEP BIOL CHEM, UNIV MD SCH MED, BALTIMORE, MD 21201, USA**
USA

JOURNAL: Archives of Biochemistry and Biophysics 192 (2): p380-390 1979

ISSN: 0003-9861

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: dolichol-bound trisaccharide, in which the glycosyl group is linked via a pyrophosphate bridge, when chromatographed on SG-81 paper or DEAE-cellulose. Mild acid *treatment* releases a water-soluble product

that comigrates with authentic .beta.-Man-(1 .fwdarw. 4)-.beta.-GlcNAc(1 .fwdarw. 4)-GlcNAc. The free [14C]trisaccharide is...

...N-acetyl[14C] glucosaminylpyrophosphoryldolichol to form [14C]disaccharide lipid. The biosynthesis of [14C]disaccharide lipid is stimulated by unlabeled UDP-N-acetylglucosamine under conditions that *inhibit* N-acetylglucosaminylpyrophosphoryldolichol synthesis. Unlike the formation of N-acetylglucosaminylpyrophosphoryldolichol the enzymatic addition of the 2nd N-acetylglucosamine residue is not *inhibited* by *tunicamycin*. Exogenous purified [14C]disaccharide lipid is enzymatically mannosylated by calf brain membranes to form the [14C]trisaccharide lipid. The formation of the [14C]trisaccharide lipid from exogenous [14C]disaccharide lipid is stimulated by unlabeled GDP-mannose and Mg2+, and *inhibited* by EDTA. Exogenous dolichyl monophosphate is also *inhibitory*. The calf brain mannosyltransferase involved in the synthesis of the trisaccharide lipid evidently requires a divalent cation and utilizes GDP-mannose, not mannosylphosphoryldolichol, as the...

...REGISTRY NUMBERS: *TUNICAMYCIN*; ...

...MANNOSYL *TRANSFERASE*

DESCRIPTORS: CALF BRAIN EDTA *TUNICAMYCIN* GDP MANNOSE METABOLIC-DRUG
CARBON-14 N N DI ACETYL CHITOBIOSE UDP N ACETYL GLUCOSAMINE N ACETYL
CARBON-14 GLUCOSAMINYL PYRO PHOSPHORYL DOLICHOL CARBON-14 N N DI ACETYL
CHITOBIOSYL PYRO PHOSPHORYL DOLICHOL GDP MANNOSE BETA MANNOSIDASE LIPID N
ACETYL GLUCOSAMINE MANNOSYL *TRANSFERASE* CHROMATOGRAPHY

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Artiodactyla, Mammalia, Vertebrata, Chordata,
Animalia

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: ...*TUNICAMYCIN*; ...

...MANNOSYL *TRANSFERASE*

6/3,K/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2006 BIOSIS. All rts. reserv.

0002441346 BIOSIS NO.: 197866027830

**THE EFFECT OF *TUNICAMYCIN* AN *INHIBITOR* OF PROTEIN GLYCOSYLATION ON
EMBRYONIC DEVELOPMENT IN THE SEA-URCHIN**

AUTHOR: SCHNEIDER E G (Reprint); NGUYEN H T; LENNARZ W J

AUTHOR ADDRESS: LAB MOL AGING, GERONTOL RES CENT, BALTIMORE CITY HOSP, 4940
EASTERN AVE, BALTIMORE, MD 21224, USA**USA

JOURNAL: Journal of Biological Chemistry 253 (7): p2348-2355 1978

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

**THE EFFECT OF *TUNICAMYCIN* AN *INHIBITOR* OF PROTEIN GLYCOSYLATION ON
EMBRYONIC DEVELOPMENT IN THE SEA-URCHIN**

ABSTRACT: A *transferase* that catalyzes the synthesis of N-acetylglucosaminyl(pyro)phosphoryldolichol from UDP-N-acetylglucosamine and endogenous dolichol phosphate was found in membranes prepared from embryos of Arbacia punctulata. N-acetylglucosaminyl(pyro)phosphoryldolichol synthesis by this membrane *transferase* is stimulated 16-fold by exogenous dolichol phosphate. The addition of *tunicamycin* to isolated membranes results in almost total

inhibition of the enzyme. Membranes isolated from embryos *treated* in vivo with *tunicamycin* exhibit no detectable *transferase* activity. This antibiotic has no effect, either in vitro or in vivo, on the enzyme that synthesizes mannosylphosphoryldolichol. When embryos are *treated* with *tunicamycin* early in development, e.g., as early as 5 h after fertilization, no morphological effects on development are observed until early gastrula, where development is...

...cell stage to early gastrula. It is only at the gastrula stage, when extensive morphogenetic movements of mesenchymal cells begins, that the effect of prior *treatment* with *tunicamycin* becomes apparent. *Treatment* of embryos with *tunicamycin* after gastrulation results in the arrest (or retardation) of spicule formation and arm growth. Spicule formation is temporally correlated with enhanced incorporation of [3H]glucosamine and $^{45}\text{Ca}^{2+}$ into macromolecules, and the extent of *tunicamycin* *inhibition* of spicule (arm) growth is roughly proportional to the extent of *inhibition* of [3H]glucosamine incorporation. The experimental results suggest an essential role for glycoproteins synthesized by the lipid-linked pathway at specific stages during embryonic development. The effects of *tunicamycin* on morphogenesis are discussed with regard to the possible production of cell surface and/or extracellular proteins deficient in carbohydrate side chains.

...REGISTRY NUMBERS: *TUNICAMYCIN*; ...

...*TRANSFERASE*

DESCRIPTORS: ARBACIA-PUNCTULATA TRITIATED GLUCOSAMINE CALCIUM-45 N ACETYL GLUCOSAMINYL PYRO PHOSPHORYL DOLICHOL MANNOSYLPHOSPHORYL DOLICHOL UDP N ACETYL GLUCOSAMINE *TRANSFERASE* GLYCO PROTEIN SYNTHESIS GASTRULA MORPHOGENESIS MEMBRANE/

DESCRIPTORS:

...BIOSYSTEMATIC NAMES: Echinodermata, Invertebrata, *Animalia*

COMMON TAXONOMIC TERMS: *Animals*;

CHEMICALS & BIOCHEMICALS: *TUNICAMYCIN*; ...

...*TRANSFERASE*

6/3,K/17 (Item 1 from file: 24)

DIALOG(R)File 24:CSA Life Sciences Abstracts

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0000311050 IP ACCESSION NO: 807212

Induction of DNA polymerase alpha and terminal deoxynucleotidyl *transferase* in the *human* lymphoblastoid cell line molt-4 by the immunomodulator bestatin.

Leyhausen, G; Dippold, W; Zahn, RK; Meyer zum Bueschenfelde, K-H; Umezawa, H; Mueller, WEG
Inst. Physiol. Chem., Univ. Mainz, Duesbergweg, FRG

Immunopharmacology, v 7, n 3-4, p 151-157, 1984

ADDL. SOURCE INFO: Immunopharmacology, vol. 7, no. 3-4, pp. 151-157, 1984

PUBLICATION DATE: 1984

DOCUMENT TYPE: Journal Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ISSN: 0162-3109

FILE SEGMENT: Immunology Abstracts; Nucleic Acids Abstracts

Induction of DNA polymerase alpha and terminal deoxynucleotidyl *transferase* in the *human* lymphoblastoid cell line molt-4 by the immunomodulator bestatin.

ABSTRACT:

The influence of the immunomodulator bestatin on the expression of terminal deoxynucleotidyl *transferase* and of DNA polymerase alpha and beta in Molt-4 cells has been studied. Bestatin was found to stimulate cell growth within the range of 0.3-33 mu M, while concentrations higher than 300 mu M were *inhibitory* during an incubation period of 48 h. The cell surface bound microsomal leucine aminopeptidase (bestatin receptor) activity decreased gradually during incubation at concentrations of bestatin above 3 mu M. This effect was also observed after incubation with amastatin, but not with leupeptin or *tunicamycin*. Determinations of the activities of DNA synthesizing enzymes from bestatin-*treated* Molt-4 cells revealed a direct correlation between the decrease of the surface bound microsomal leucine aminopeptidase activity and the increase of the terminal deoxynucleotidyl *transferase* and DNA polymerase alpha activity; the DNA polymerase beta activity remained unchanged. From these experiments it is hypothesized that bestatin might cause a promoting effect...

6/3,K/18 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.

07090993 Genuine Article#: 122TR No. References: 53
Title: A functional link between N-linked glycosylation and apoptosis in Chinese hamster ovary cells
Author(s): Walker BK; Lei H; Krag SS (REPRINT)
Corporate Source: JOHNS HOPKINS UNIV, SCH HYG & PUBL HLTH, DEPT BIOCHEM, 615 N WOLFE ST/BETHESDA//MD/20205 (REPRINT); JOHNS HOPKINS UNIV, SCH HYG & PUBL HLTH, DEPT BIOCHEM/BETHESDA//MD/20205
Journal: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 1998, V250, N2 (SEP 18), P264-270
ISSN: 0006-291X Publication date: 19980918
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

...Abstract: not in all of them (MI5-4 and MI8-5), incubation at 40.5 degrees C induced apoptosis, as determined by appearance of DNA fragmentation. *Tunicamycin* (TRI) also induced apoptosis in both parental and Lec9 cells. There was a direct correlation between *inhibition* of glycosylation by TRI *treatment* and induction of apoptosis. Induction of apoptosis by TM was *inhibited* by cycloheximide. These studies suggest that specific alterations in N-linked glycosylation in CHO cells are endogenous inducers of apoptosis. (C) 1998 Academic Press.
...Identifiers--ACETYLGLUCOSAMINYLTRANSFERASE ACTIVITY; *TRANSFERASE* -ACTIVITY; CYTOCHROME-C; *ANIMAL*-CELLS; DEATH; *TUNICAMYCIN*; *PROTEIN*; BCL-2; RESISTANT; MUTANTS

6/3,K/19 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.

06360198 Genuine Article#: YM055 No. References: 39
Title: Enhanced stimulatory adenyllyl cyclase signaling during opioid

dependence is associated with a reduction in palmitoylated G(s alpha)
Author(s): Ammer H (REPRINT) ; Schulz R
Corporate Source: UNIV MUNICH, INST PHARMACOL TOXICOL & PHARM, KOENIGINSTR
16/D-80539 MUNICH//GERMANY/ (REPRINT)
Journal: MOLECULAR PHARMACOLOGY, 1997, V52, N6 (DEC), P993-999
ISSN: 0026-895X Publication date: 19971200
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Abstract: Chronic opioid *treatment* of stably mu-opioid receptor
transfected *human* mammary epidermoid A431 carcinoma cells (clone
A431/mu 13) results in sensitization of adenylyl cyclase (AC), a
cellular adaptation associated with drug dependence. Up-regulation...

...in the quantity of stimulatory G proteins and the maximum catalytic
activity of AC. Here, we report that detergent extracts from membranes
of chronically morphine-*treated* (10 mu M; 2 days) A431/mu 13 cells
display higher stimulatory AC activities as assessed in the S49cyc(-)
reconstitution assay. This finding is most...
...subunits, which per se stimulate AC in S49cyc(-) membranes, failed to
affect the difference in reconstitutive AC activity. Moreover, both
chemical depalmitoylation by hydroxylamine and *inhibition* of
palmitoyl-CoA *transferase* in vivo by *tunicamycin* *treatment*
increased the reconstitutive activity of detergent extracts and
eliminated the differences between native and opioid-dependent cells,
indicating that the increase in stimulatory activity is due to
depalmitoylation of G(S alpha). Indeed, metabolic labeling studies with
[H-3]palmitic acid revealed that chronic opioid *treatment* reduces
considerably the fraction of palmitoylated G(S alpha) in the plasma
membrane. Furthermore, high affinity [H-3]forskolin binding experiments
demonstrated that depalmitoylated G...

6/3,K/20 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.

05507858 Genuine Article#: WC820 No. References: 33
**Title: Short exposures to *tunicamycin* induce apoptosis in
SV40-transformed but not in normal *human* fibroblasts**
Author(s): Carlberg M (REPRINT) ; Dricu A; Blegen H; Kass GEN; Orrenius S;
Larsson O
Corporate Source: KAROLINSKA INST, DEPT TUMOR PATHOL/S-17177
STOCKHOLM//SWEDEN/ (REPRINT); UNIV SURREY, SCH BIOL SCI/GUILDFORD GU2
5XH/SURREY/ENGLAND/; KAROLINSKA INST, INST ENVIRONM MED, DIV
TOXICOL/S-17177 STOCKHOLM//SWEDEN/
Journal: CARCINOGENESIS, 1996, V17, N12 (DEC), P2589-2596
ISSN: 0143-3334 Publication date: 19961200
Publisher: OXFORD UNIV PRESS UNITED KINGDOM, WALTON ST JOURNALS DEPT,
OXFORD, ENGLAND OX2 6DP
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

**Title: Short exposures to *tunicamycin* induce apoptosis in
SV40-transformed but not in normal *human* fibroblasts**

Abstract: When SV40-transformed fibroblasts (line 90VAVI) were exposed to
tunicamycin, an *inhibitor* of N-linked glycosylation, an extensive
cell death occurred compared with untransformed fibroblasts. A
considerable cell loss was obtained within 24 h after *tunicamycin*
addition, and after 72 h there were hardly any virus-transformed cells
alive. A 2-h pulse *treatment* with tunicamycin was found to be almost
as effective as a continuous 48-h *treatment* in killing the cells,

Even such a short exposure as 7 min resulted in a drastically decreased cell viability (54%). The morphology of the dying *tunicamycin*-
treated 90VAVI cells suggested that they were undergoing apoptosis. This was also supported by the appearance of nuclear condensation, as assayed by propidium iodide uptake, which was detectable within 2 h after *tunicamycin* addition. Furthermore, analysis of DNA from *tunicamycin*-
treated 90VAVI cells by field inversion gel electrophoresis revealed DNA degradation into 50 kbp fragments within 2 h, and conventional agarose gel electrophoresis showed 'DNA laddering', indicating internucleosomal DNA cleavage, detectable after 36 h. Together with the finding that *tunicamycin* within seconds caused an elevation of [Ca²⁺]_i, a well documented early feature of apoptosis in many experimental systems, these results strongly suggest that *tunicamycin*-induced cell death in 90VAVI is due to apoptosis. The short *tunicamycin* exposure required to trigger cell death in 90VAVI indicates that the apoptotic process is irreversibly induced soon after its addition. It seems unlikely that the...

...could be depleted during such a short period. Instead the overall accumulation of unglycosylated proteins in ER might contribute to the apoptotic response in 90VAVI. *Tunicamycin* also killed and induced DNA degradation in the breast cancer cell line MDA-231.

Research Fronts: 95-1076 002 (INTERNUCLEOSOMAL DNA FRAGMENTATION DURING DRUG-INDUCED APOPTOSIS; PROGRAMMED CELL-DEATH; APOPTOTIC BODIES)
95-1809 001 (POTENT *INHIBITORS* OF RAS FARNESYL-PROTEIN *TRANSFERASE*; NUCLEAR LAMIN ISOPRENYLATION IN XENOPUS OOCYTES; PRENYLATION SIGNAL SEQUENCES)
95-3190 001 (INCREASED ABUNDANCE OF SPECIFIC SKELETAL-MUSCLE PROTEIN-TYROSINE PHOSPHATASES; ALPHA-B-CRYSTALLIN EXPRESSION...

6/3,K/21 (Item 4 from file: 34)
DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.

04475740 Genuine Article#: TF460 No. References: 62

Title: SIZE VARIATIONS IN THE MUCIN-TYPE DOMAIN OF HAMSTER OVIDUCTIN - IDENTIFICATION OF THE POLYPEPTIDE PRECURSORS AND CHARACTERIZATION OF THEIR BIOSYNTHETIC MATURATION

Author(s): MALETTE B; PAQUETTE Y; BLEAU G

Corporate Source: MAISONNEUVE ROSEMONT MED CTR, RECH REPROD HUMAINE GRP, 5415 BLVD ASSOMPT/MONTREAL/PQ H1T 2M4/CANADA/; MAISONNEUVE ROSEMONT MED CTR, RECH REPROD HUMAINE GRP/MONTREAL/PQ H1T 2M4/CANADA/; UNIV MONTREAL, DEPT BIOCHEM/MONTREAL/PQ/CANADA/; UNIV MONTREAL, DEPT OBSTET & GYNECOL/MONTREAL/PQ/CANADA/

Journal: BIOLOGY OF REPRODUCTION, 1995, V53, N6 (DEC), P1311-1323

ISSN: 0006-3363

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: type domain. This domain contains contiguous Ser/Thr-rich repeated stretches of 15 amino acids; similar units are also found in the deduced sequence of *human* oviductin. Such structural domains constitute a central feature of mucins. We amplified this region from 16 hamster oviductin cDNA clones and identified three length variants

...derived from internal sequences of hamster oviductin was produced and used in pulse-chase experiments. Two major and one minor polypeptide precursors were identified from *tunicamycin*-
treated cell lysates and in vitro translated products from oviductal poly(A)(+) RNA. Their apparent molecular masses correlate with the predicted lengths of the three size variants identified by polymerase chain reaction (PCR)

amplification. Using glycosylation and transport *inhibitors*, we sought to dissect the posttranslational sequential steps leading to the final maturation of hamster oviductin and proposed a compartmental model for its biosynthesis. The...

Research Fronts: 93-1639 003 (GOLGI MEMBRANES; BREFELDIN-A *INHIBITS* PROTEIN-SYNTHESIS; SYCAMORE MAPLE (ACER-PSEUDOPLATANUS) SUSPENSION-CULTURED CELLS)

93-0615 001 (HIGHLY POLYMORPHIC MICROSATELLITE LOCI; DNA FINGERPRINTING; SIMPLE SEQUENCE REPEATS; PATERNITY TESTING; ALLELES IN ...

...TRIAL OF HIGH-DOSE INTERLEUKIN-2; ADOPTIVE CELLULAR THERAPY; HLA-A2 MATCHED ALLOGENEIC MELANOMA-CELLS)

93-3088 001 (RAT MUSCLE; PROTEIN PHOSPHATASE-1; MAJOR GLUTATHIONE *TRANSFERASE*)

93-4046 001 (PEA LECTIN; TRANSGENIC TOBACCO PLANTS; ALPHA-AMYLASE *INHIBITOR*; CHITIN-BINDING PROTEINS)

6/3,K/22 (Item 5 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.

04087633 Genuine Article#: RD800 No. References: 45

Title: ANTIDIABETIC AGENT PIOGLITAZONE INCREASES INSULIN-RECEPTORS ON 3T3-L1 ADIPOCYTES

Author(s): SWANSON ML; BLEASDALE JE

Corporate Source: UPJOHN CO, ENDOCRINE PHARMACOL & METAB, 7250-126-3, 301 HENRIETTA ST/KALAMAZOO//MI/49007; UPJOHN CO, ENDOCRINE PHARMACOL & METAB/KALAMAZOO//MI/49007

Journal: DRUG DEVELOPMENT RESEARCH, 1995, V35, N2 (JUN), P69-82

ISSN: 0272-4391

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: to overcome insulin resistance by affecting an unidentified early event in insulin action. Because attempts to determine changes in insulin receptors in tissues from thiazolidinedione-*treated* diabetic *animals* are complicated by drug-induced reduction of hyperinsulinemia and consequent receptor up-regulation, 3T3-L1 cells were utilized here as an in vitro model system...

...the culture medium, there was an increase in specific binding of insulin to the cell surface that was further augmented 25 and 47% in cells *treated* with pioglitazone for 12 and 24 h, respectively (EC(50) about 0.6 mu M, maximal at 5-25 mu M). Pioglitazone increased the number...

...3-phosphate dehydrogenase activity, a marker of adipocyte differentiation, was also increased in a dose-dependent manner by pioglitazone (maximal at 10-25 mu M). *Tunicamycin*, which *inhibits* the N-linked glycosylation of newly synthesized insulin receptors that is required for their translocation to the cell surface, decreased specific insulin binding by about...

Research Fronts: 93-3088 002 (RAT MUSCLE; PROTEIN PHOSPHATASE-1; MAJOR GLUTATHIONE *TRANSFERASE*)

93-8243 001 (GENE AMPLIFICATION; N-LINKED CARBOHYDRATE CHAINS PROTECT LACCASE-III)

6/3,K/23 (Item 6 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04076825 Genuine Article#: RC770 No. References: 35

**Title: EXPRESSION AND CHARACTERIZATION OF MURINE OSTEOBLAST-SPECIFIC
FACTOR-2 (OSF-2) IN A BACULOVIRUS EXPRESSION SYSTEM**

Author(s): SUGIURA T; TAKAMATSU H; KUDO A; AMANN E

Corporate Source: MASSACHUSETTS GEN HOSP, DEPT MOLEC BIOL/BOSTON//MA/02114;
HOECHST JAPAN LTD, PHARMA RES LABS, MOLEC BIOL LAB/KAWAGOE/SAITAMA
35011/JAPAN/

Journal: PROTEIN EXPRESSION AND PURIFICATION, 1995, V6, N3 (JUN), P305-311
ISSN: 1046-5928

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Abstract: Osteoblast-specific factor 2 (OSF-2) is a similar to 90-kDa protein selectively expressed in bone. OSF-2 cDNA was recently isolated from *mouse* and *human* cDNA libraries and shows limited sequence homology with fasciclin I, a cell adhesion protein expressed in insect nerve cells. Here we describe the expression of...

...OSF-2 peptide detected a protein of similar to 90-kDa as early as 2 days after infection of Sf9 cells with the recombinant virus, *Tunicamycin* treatment of infected cells resulted in a mobility shift of OSF-2 (similar to 90-kDa band) on Western blots, N-Glycanase digestion resulted in the...

Research Fronts: 93-3088 002 (RAT MUSCLE; PROTEIN PHOSPHATASE-1; MAJOR GLUTATHIONE *TRANSFERASE*)

93-0104 001 (BASIC FIBROBLAST GROWTH-FACTOR; VASCULAR CELL-DERIVED HEPARAN-SULFATE SHOWS COUPLED *INHIBITION*; FUNCTIONAL SPECIFICITY OF FGF RECEPTORS)

93-0736 001 (TRANSFORMING GROWTH-FACTOR-BETA; EXPRESSION OF TYPE-II ACTIVIN RECEPTOR GENES; RAT SERTOLI CELLS)

93-2767 001...

...AUTOGRAPHICA-CALIFORNICA NUCLEAR POLYHEDROSIS-VIRUS; RECOMBINANT VIRAL INSECTICIDES)

93-4847 001 (HETEROLOGOUS EXPRESSION; CHROMOSOMAL DNA; GENE ENCODING METHYLMALONYL-COENZYME-A MUTASE)

93-5989 001 (EARLY *HUMAN* HEMATOPOIETIC PROGENITORS; BONE-MARROW STROMAL CULTURES; RELEASE OF MATRIX-BOUND BASIC FIBROBLAST GROWTH-FACTOR; ADHESION MOLECULES)

93-8243 001 (GENE AMPLIFICATION; N-LINKED CARBOHYDRATE CHAINS...

6/3,K/24 (Item 1 from file: 71)

DIALOG(R) File 71:ELSEVIER BIOBASE

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02906823 2005061366

The effects of N-glycosylation sites and the N-terminal region on the biological function of beta1,3-N-acetylglucosaminyltransferase 2 and its secretion

Kato T.; Suzuki M.; Murata T.; Park E.Y.

ADDRESS: E.Y. Park, Dept. of Appl. Biological Chemistry, Faculty of Agriculture, Shizuoka University, 836 Ohya, Shizuoka 422-8529, Japan

EMAIL: yspark@agr.shizuoka.ac.jp

Journal: Biochemical and Biophysical Research Communications, 329/2 (699-705), 2005, United States

PUBLICATION DATE: April 8, 2005

CODEN: BBRCA

ISSN: 0006-291X

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 26

Human beta1,3-N-acetylglucosaminyltransferase 2 (beta3GnT2) is thought to be an enzyme that extends the polylactosamine acceptor chains, but its function and structure analysis are unknown. To obtain insight into the structure of beta3GnT2, the effects of N-glycosylation on its biological function were evaluated using the addition of ***inhibitors***, site-directed mutagenesis of potential N-glycosylation sites, and deletion of its N-terminal region using a fusion protein with GFPSUBuv in a baculovirus expression system. Four of five potential N-glycosylation sites were found to be occupied, and their biological function and secretion were ***inhibited*** with the ***treatment*** of N-glycosylation ***inhibitor***, ***tunicamycin***. The N-glycosylation at Asn219 was necessary for the beta3GnT activity; moreover, N-glycosylation at Asn127 and Asn219 was critical for efficient protein secretion. When...

CLASSIFICATION CODE AND DESCRIPTION:
...***TRANSFERASES*** (EC 2

6/3,K/25 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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Characterization of a R115777-resistant *human* multiple myeloma cell line with cross-resistance to PS-341

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Characterization of a R115777-resistant *human* multiple myeloma cell line with cross-resistance to PS-341

The farnesyl ***transferase*** ***inhibitor*** R115777 has been found to have clinical activity in diverse hematopoietic tumors. Clinical efficacy, however, does not correlate with Ras mutation status or ***inhibition*** of farnesyl ***transferase***. To further elucidate the mechanisms by which R115777 induces apoptosis and to investigate drug resistance, we have identified and characterized a R115777-resistant ***human*** myeloma cell line. 8226/R5 cells were found to be at least 50 times more resistant to R115777 compared with the parent cell line 8226/S. K-Ras remained prenylated in both resistant and sensitive cells after R115777 ***treatment***; however, HDJ-2 farnesylation was ***inhibited*** in both lines, implying that farnesyl ***transferase*** (the drug target) has not been mutated. Whereas many 8226 lines that acquire drug resistance have elevated expression of P-glycoprotein, we found that P...

DRUG DESCRIPTORS:

protein farnesyltransferase ***inhibitor***--pharmacology--pd; heat shock protein--endogenous compound--ec; glycoprotein P--endogenous compound--ec; n [[5 [(2 amino 3 mercaptopropyl)amino][1,1' biphenyl] 2 yl]carbonyl]methionine methyl ester; doxorubicin; melphalan; perilllic acid;

staurosporine; etoposide; *tunicamycin*

MEDICAL DESCRIPTORS:

cancer cell culture; apoptosis; oncogene K ras; prenylation; drug targeting
; multidrug resistance; phenotype; gene expression; drug accumulation; drug
mechanism; *human*; controlled study; *human* cell; article; priority
journal

...CAS REGISTRY NO.: 7694-45-3 (perillic acid); 62996-74-1 (staurosporine);
33419-42-0 (etoposide); 11089-65-9 (*tunicamycin*)

6/3,K/26 (Item 2 from file: 73)

DIALOG(R)File 73:EMBASE

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02493730 EMBASE No: 1983087741

**Selective cytotoxicity of purified homologues of *tunicamycin* on
transformed BALB/3T3 fibroblasts**

Seiberg M.; Duksin D.

Dep. Biophys., Weizmann Inst. Sci., Rehovot 76100 Israel

Cancer Research (CANCER RES.) (United States) 1983, 43/2 (845-850)

CODEN: CNREA

DOCUMENT TYPE: Journal

LANGUAGE: ENGLISH

**Selective cytotoxicity of purified homologues of *tunicamycin* on
transformed BALB/3T3 fibroblasts**

The selective cytotoxicity of *tunicamycin* homologues against
SV40-transformed 3T3 cells (SV40-3T3) was examined. Incubation of 3T3 or
virally transformed 3T3 cells with four different homologues (Ainf 1, Ainf
...

...cells occurred only when higher doses (at least 5-fold) of Ainf 2-, Binf
1-, and Binf 2-tunicamycins were used. In contrast, these homologues
inhibited proliferation of 3T3 cells, even when doses of 0.5 mug/ml were
used. These cytotoxic effects are dose dependent, and maximal cytotoxicity
of each homologue is achieved at a different concentration in each cell
type. These results indicate that *tunicamycin* homologues have selective
cytotoxicity against transformed cells. Incorporation of (sup 3H)mannose
into acid-precipitable macromolecules synthesized by transformed cells was
strongly *inhibited* (70 to 75%) by Ainf 1- and Binf 2-tunicamycins at 0.01
to 0.05 mug/ml, while incorporation by 3T3 cells was not...

...At higher concentrations of the above tunicamycins (0.5 to 1 mug/ml),
(sup 3H)mannose incorporation by both 3T3 and SV40-3T3 cells was
inhibited more than 95%. In contrast, the effect of these *tunicamycin*
homologues on protein synthesis in 3T3 and SV40-3T3 fibroblasts was less
pronounced since the incorporation of amino acids was *inhibited* by
approximately 20%. Very little *inhibition* of amino acid incorporation
occurred when 3T3 or SV40-3T3 cells were *treated* with Binf 2-
tunicamycin. However, Ainf 1-*tunicamycin* *inhibited* (sup 3H)proline
incorporation and slightly increased (sup 3H)tyrosine incorporation into
cell layers of 3T3 cells. Examination of secreted proteins synthesized by
these cells on sodium dodecyl sulfate:polyacrylamide gel electrophoresis
revealed that both 3T3 and SV40-3T3 cells *treated* with homologues
produced partially glycosylated macromolecules, such as procollagen and
fibronectin, and failed to convert procollagen to collagen. *Tunicamycin*
homologues also *inhibited* the N-acetylglucosamine-1-phosphate
transferase activity found in microsomes prepared from 3T3 and virally
transformed 3T3 fibroblasts. The data presented indicate that the cytotoxic

activity of purified homologues of *tunicamycin* against transformed fibroblasts might be due to the selective *inhibition* of glycosylation and to the differences in the membrane solubilities of the homologues.

DRUG DESCRIPTORS:

****tunicamycin***

MEDICAL DESCRIPTORS:

protein synthesis; simian virus 40; intoxication; nonhuman; *mouse*; in vitro study

CAS REGISTRY NO.: 11089-65-9 (*tunicamycin*)

6/3,K/27 (Item 1 from file: 94)

DIALOG(R)File 94:JICST-EPlus

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03588424 JICST ACCESSION NUMBER: 98A0605179 FILE SEGMENT: JICST-E

Changes of Gene Expression by Lysophosphatidylcholine in Vascular

Endothelial Cells: 12 Up-Regulated Distinct Genes Including 5 Cell Growth-Related, 3 Thrombosis-Related, and 4 Others.

SATO N (1); KOKAME K (1); SHIMOKADO K (1); KATO H (1); MIYATA T (1)

(1) National Cardiovascular Center Res. Inst., Osaka

J Biochem, 1998, VOL.123,NO.6, PAGE.1119-1126, FIG.4, TBL.1, REF.44

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...ABSTRACT: proatherogenic properties have been demonstrated. To gain an insight into lysoPC-mediated endothelial gene expression, we applied nonradioactive differential display analysis of mRNA from lysoPC-*treated* and untreated *human* umbilical vein endothelial cells. We identified 12 up-regulated distinct genes including 5 cell growth-related genes (two phosphatases CL100 and B23/hVH-3, gravin, activating transcription factor-4, and heparin-binding epidermal growth factor-like growth factor), 3 thrombosis-related genes (plasminogen activator *inhibitor*-1, tissue plasminogen activator, and thrombomodulin), and 4 others (stanniocalcin, NAD-dependent methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase, BENE, and reducing agents and *tunicamycin*-responsive protein). We isolated a full-length cDNA of *human* gravin. The cDNA sequence of gravin was homologous with rat mitogenic regulatory gene or rat protein kinase C binding protein and substrate, suggesting that gravin...

DESCRIPTORS: *human*(primates...

...BROADER DESCRIPTORS: *animal* protein...

...enzyme *inhibitor*; ...

...*transferase*;

6/3,K/28 (Item 1 from file: 98)

DIALOG(R)File 98:General Sci Abs

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04751945 H.W. WILSON RECORD NUMBER: BGSA02001945 (USE FORMAT 7 FOR FULLTEXT)

The action of molecular chaperones in the early secretory pathway.

Fewell, Sheara W

Travers, Kevin J; Weissman, Jonathan S
Annual Review of Genetics v. 35 (2001) p. 149-91
SPECIAL FEATURES: bibl il ISSN: 0066-4197
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 20822

(USE FORMAT 7 FOR FULLTEXT)

TEXT:

... similar]70 amino acid sequence called the J domain that mediates Hsc70 interaction. Structural studies of the J domains from bacterial DnaJ (106, 193, 242), *human* Hdjlp (203) and the SV40 and polyomavirus large T antigens (14, 131) indicate that this domain folds into four α -helices, two of which are...the ER (84). Consistent with this model, mutations in BiP that prevent an ATP-dependent conformational change and interaction with Sec63p, but not peptide binding, *inhibit* translocation both in vivo and in vitro in a dominant manner (152). The motor model may also be supported by the observations that mitochondrial Hsp70...Hsp70 activity exhibit protein folding defects (228a) and synthetic interactions with mutated alleles of genes encoding the luminal Hsp40 chaperones and components of the oligosaccharyl *transferase* (179, 218, 242a). BiP most likely aids folding by preventing off-pathway intermediates from forming. Both BiP and another Hsp70 homologue in yeast, Lhs1p (Hsp170...For example, the chemical steps involved in disulfide bond formation and rearrangement are intrinsically slow compared to conformational rearrangements. Moreover, partial native structure can dramatically *inhibit* access to buried cysteines, further slowing disulfide rearrangement (264). Similarly, transmembrane domains must be inserted with correct topology into the ER membrane if a protein...

...for proper oxidative protein folding (72, 201). Central to these studies is the fact that the redox balance of living cells can be manipulated through *treatment* with the membrane-permeable reducing agent dithiothreitol (DTT) (22, 119). Whereas wild-type cells tolerate limited quantities of DTT, cells with defective oxidation machinery exhibit... Consistent with previous suggestions from studies of the influenza hemagglutinin (HA) protein (112), these results indicate that the ER may form a dense matrix that *inhibits* the movement of normally mobile proteins. With VSVG, the aggregates were held together by disulfide bonds, as mobility could be restored through *treatment* of the cells with DTT (175).

In their studies of the subcellular localization of VSVG by indirect immunofluorescence, Hammond & Helenius provide another suggestion for how ...genes encoding BiP and calnexin exhibit increased resistance to the K28 killer toxin (64), and prior to export, PDI is required for toxin unfolding (246). *Inhibition* of proteasome activity sensitizes both yeast and mammalian cells to toxins (229, 266), suggesting that a fraction of the retro-translocated toxin is recognized as...

...and Hrd1p, respectively, factors involved in ERAD (20, 133). Finally, mutants that accumulate a heterologously expressed variant of the mammalian ERAD substrate. Alpha-1 protease *inhibitor* (AlPiZ; 204), have identified seven complementation groups that may represent novel genes involved in ERAD (155). Combining the continued analysis of these and other genes...

...of proteins in response to glucose starvation, which results in protein misfolding through the under-glycosylation of nascent polypeptides (39). The proteins induced through this *treatment* were designated GRPs as a consequence of their glucose regulation (e.g., GRP78 was the original name given to BiP), and consisted largely of molecular chaperones. Other

treatments were soon discovered that increased the transcription of the same set of genes, including *tunicamycin* (an *inhibitor* of N-linked glycosylation), DTT, and calcium-ionophores. However, other general stress conditions, including heat shock, do not induce the expression of the same set...

...that in *S. cerevisiae* and has been less clearly defined. A number of groups have identified Irep homologs in higher eukaryotes, including Ire1a (identified in *humans*) (243), Ire1b (identified in *mouse* cells) (258), and PERK (98, 225). Whereas both Ire1a and Ire1b show homology to Irep throughout their entire lengths, PERK is homologous to Irep only... transcription factor responsible for the ER stress response in metazoan cells. ATF6, a Type-II transmembrane protein, is cleaved into two fragments in response to *treatments* that lead to the accumulation of misfolded proteins, and the released cytosolic domain translocates into the nucleus and induces the transcription of several chaperones (31...54

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03253323 H.W. WILSON RECORD NUMBER: BGS196003323 (USE FORMAT 7 FOR FULLTEXT)

Genetic analysis of the multidrug transporter.

Gottesman, M. M

Hrycyna, C. A; Schoenlein, P. V

Annual Review of Genetics (Annu Rev Genet) v. 29 ('95) p. 607-49

SPECIAL FEATURES: bibl il ISSN: 0066-4197

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(USE FORMAT 7 FOR FULLTEXT)

ABSTRACT: The genetic and molecular genetic analysis of the *human* multidrug transporter may reveal a mechanism for the evasion of *human* cancers from chemotherapy. The multidrug transporter is a genetic alteration that increases expression of an ATP-dependent plasma membrane transport system. Also known as P...

...expression, and the properties of transgenic and "knock-out" mice. The role of the MDR gene, which encodes P-glycoprotein, as a selective marker for *human* gene therapy is also discussed.

TEXT:

... whether such alterations are responsible for drug resistance in the cancers of patients who are unresponsive to chemotherapy, either (a) because of acquired resistance following *treatment* with anticancer drugs, or (b) as part of the intrinsic drug-resistance mechanisms of the patients' cancer cells. However, overexpression of an energy-dependent transport...

...in cultured cancer cells. The MDR1 gene, which encodes P-gp, is expressed at levels thought to be physiologically significant in about 50[percent] of *human* cancers (91, 96).

Reviews of various aspects of the biochemistry (96), clinical significance and reversal of function (19, 94, 144), evolution (26, 71), and regulation of expression (49) of the P-gps have appeared in the past two years. Thus, this review focuses on genetic analysis of the *human* MDR1 gene, and where necessary reference is made to these and other recent reviews on the biochemistry, pharmacology, physiology, and cell biology of the multidrug...

...not be limiting for drug resistance in cancer, but may be essential for drug resistance mediated by alterations in glutathione levels and levels of glutathione *transferases* and/or other conjugating systems. Both the MDR1 and MRP genes belong to a superfamily of ATP-dependent transporters (the ATP-Binding Cassette, or ABC...

...THE MULTIDRUG TRANSPORTER

Although simultaneous resistance to many anticancer drugs had been appreciated as a cause of failure of chemotherapy since the introduction of multiagent *treatment* of cancer, the first cell lines shown to become simultaneously resistant to anticancer drugs were not reported until the late 1960s. The pioneering work of...

...genes were amplified in these lines (78). Shortly thereafter, an in-gel renaturation technique was used to identify and isolate amplified segments of DNA in *human* MDR adenocarcinoma (KB) cells (192) and in DNA-mediated

MDR transformants (214), which allowed for the detection of increased levels of a specific MDR1 mRNA (217). Cloning and sequencing of the MDR1 cDNA and its two homologs in the *mouse* (mdr1a and mdr1b, also called mdr3 and mdr1) established that the *human* MDR1 cDNA encoded the 1280-amino-acid P-gp that was homologous to other ATP-dependent transporters (the ABC family). The sequence information led to...
...isolated vesicles (58, 117). These studies established the basic mechanism by which P-gp transports drugs (by direct interaction with the transporter) and of its *inhibition* (by competition for transport sites). Recent studies in which purified P-gp has been isolated from drug-resistant cells and reconstituted into proteoliposomes have proved...

...dependent transporter capable of moving drugs across a lipid bilayer against a concentration gradient (7, 8, 212, 213).

It was not immediately clear why the *human* genome or the genomes of other mammals would house genes that conferred broad-spectrum resistance to chemically dissimilar anticancer drugs. Through use of specific ...and a specific antihuman P-gp monoclonal antibody (MRK-16) developed in the laboratory of Tsuruo (108), the tissues that normally express P-gp in *humans* were delineated (55, 77, 232, 233). Based on expression of the *human* MDR1 gene in transporting epithelia of the liver, kidney, intestine, and pancreas, in capillary endothelial cells of the brain and testis, and in adrenocortical cells...

...of action of the multidrug transporter and may have implications for other members of the ABC family of transporters.

MUTATIONAL ANALYSIS OF THE MULTIDRUG TRANSPORTER

Human P-glycoprotein (P-gp) encoded by the MDR1 gene is known to encode a 170-kDa integral membrane protein composed of two homologous halves. Each ...

...single molecule can function to transport such a wide variety of agents.

MUTATIONS AFFECTING SUBSTRATE BINDING

The major sites of interaction of three P-gp *inhibitors*, 3H-azidopine, 125I-6-AIPP-forskolin, and 125I-iodoarylazidoprazosin, have been determined by photo-affinity labelling, digestion with proteases or cyanogen bromide, and specific immunoprecipitation with antibodies directed against polypeptide epitopes of P-gp (28-30, 97, 164). Binding of these photo-affinity labels is specifically *inhibited* by P-gp substrates, including vinblastine, suggesting that they interact with major substrate interaction sites in the multidrug transporter. Equal labelling of the amino-terminal and C-terminal halves of P-gp is observed as well as equal *inhibition* of labelling by vinblastine (29). Further refinement of the binding site using 125I-6-AIPP-forskolin (164) revealed that a tryptic peptide consisting of transmembrane...

...them, and a small part of the cytoplasmic region lying between TM 6 and the amino-terminal ATP-binding site is labelled (Figure 1). In *mouse* P-gp, a comparable region around TM 11 and 12 has been found to be labelled (97). Recently, it has been found that a chimeric...

...poor labelling with 125I-iodoarylazidoprazosin. These results suggest that these regions, working either separately or in concert, are either primary binding sites for substrates and *inhibitors* or define a pathway by which the drugs move through the transporter in the plasma membrane. Importantly, drug-stimulated ATPase activity has been observed in Sf9 insect cells only when both halves of *human* P-gp are co-expressed, suggesting that the coupling of ATPase activity to drug binding and

possibly to transport requires direct interaction between the two...

...circles shown in Figure 1 represent amino acids that when mutated alter the substrate specificity of the transporter. Unless otherwise noted, mutations are in the *human* P-gp molecule and changes in drug specificity are described relative to the wild-type molecule.

The change-of-specificity mutations are found scattered throughout...

...cells most resistant to actinomycin D, whereas the wild-type gene confers highest resistance to colchicine. Loo & Clarke (140) engineered mutations into TM 6 of *human* MDR1 and transfected the cDNA into drug-sensitive NIH3T3 cells. A ...to vinblastine and actinomycin D but has no effect on resistance to colchicine and doxorubicin. The mutation of Ser to Phe in TM 11 of *mouse* mdr1 (position 941) and mdr3 (position 939) also alters the pattern of drug resistance. In mdr1, this mutation caused a drastic reduction of resistance to...

...gp activity and the binding of photo-activatable drug substrates (124). In TM 12, a Phe-to-Ala or -Ser mutation at residue 978 of *human* P-gp resulted in no resistance to colchicine and doxorubicin and in reduced resistance to vinblastine and actinomycin D. A Phe-to-Leu mutation at...

...effect, decreasing resistance to all four drugs but demonstrating a more pronounced phenotype with colchicine and doxorubicin (137).

Loo & Clarke mutated 13 proline residues in *human* P-gp, five of which are located in putative transmembrane domains (138). Interestingly, only two of these, Pro-to-Ala at positions 223 and 866...

...from Gly to Ala at positions 431 and 1073 and from Lys to Arg at positions 432 and 1074 in the Walker A motif of *mouse* mdr1 result in no detectable function, suggesting that these residues are essential for function (15). Either of the mutations alone was sufficient for inactivation, suggesting...

...that a step subsequent to ATP binding is impaired in these mutants. A Lys-to-Met mutation at either position 433 and/or 1076 in *human* P-gp severely attenuated drug-stimulated ATPase activity, but similar to the case of the *mouse* mdr1 mutations, the molecules were still able to bind 8-azido-ATP (M Muller, E Bakos, E Welker, A Varadi, UA Germann, MM Gottesman, BS...

...fibrosis transmembrane conductance regulator (CFTR) (188), which is also a member of the ABC transporter family.

An interesting mutation engineered into the C region of *human* P-gp was recently described by Hoof et al (116). In this study, another common mutation in CFTR was introduced at position 536 in the...of Pro to Ala at positions 223 and 866, in which only resistance to vinblastine remained unchanged. The results of existing photo-affinity labelling and *inhibition* studies call into question this idea, however.

The mutational data also suggest a direct interaction between the substrate-binding sites and the C region of...

...the transporter (15). Further mutational studies should help to elucidate the mechanism of action of P-gp and ultimately allow for the development of new *inhibitors* and reversing agents.

PRETRANSLATIONAL REGULATION OF MDRI GENE EXPRESSION

The tissue-specific expression of P-gp and the potential importance of regulation of the MDRI...

...and in cancer cells have stimulated studies of the regulatory biology of the MDR1 gene. The major and minor start sites for transcription of the *human* MDR1 gene have been identified (238), as have DNA sequences upstream from the major site of transcription initiation that were shown to function as a promoter in standard reporter assays (239). The *mouse*, hamster, and rat promoters for mdr genes were also identified subsequently (reviewed in 49). Interestingly, there is not a lot of sequence conservation between *human* and rodent mdr1 promoter regions, consistent with the differential expression of rodent mdr1a and mdr1b genes and with apparent differences between rodent and *human* cells in sensitivity to induction of mdr genes (see below).

In work reported by the laboratories of Cornwell (56, 61), Tsuruo (172), Baas (245), and...

...the MDR1 gene suggested that a variety of stimuli could increase levels of MDR1 RNA in different cells and tissues, including partial hepatectomy and xenobiotic *treatment* in rat liver (74, 234), heat shock and arsenite in certain cell types (50), DNA-damaging and chemotherapeutic agents (42, 48, 149, 236), sodium butyrate (160, 165), extracellular matrix (209), protein kinase C agonists (41), *inhibitors* of P-gp such as verapamil (166), and growth factors (60). Although in several cases a direct effect on transcription was suggested by nuclear runoff...

...by nuclear runoff may not exclude this mechanism of induction of MDR1 expression. For example, even though increases in nuclear runoff are not detected in *human* kidney cells exposed to heat shock (50), the MDR1 promoter appears to have a heat-shock-like consensus element that is activated in transient expression...

...progesterone-responsive element in the rodent mdr1b upstream region (177). In a recent study in which one of two mdr1b alleles was inactivated in *mouse* adrenocortical Y-1 cells, the remaining allele was overexpressed, suggesting feedback control in mdr1b-expressing tissues (6). The *human* adrenal cortex expresses very high levels of the MDR1 gene, consistent with induction by steroids in this tissue. The overall impression from these studies (and ...mechanism of this regulation is complex and still very poorly understood).

One striking regulatory feature of MDR1 expression is the high frequency of expression in *human* tumors (91). Three classes of *human* cancers express P-gp (96): (a) those derived from tissues in which the MDR1 gene is constitutively activated (e.g. colon, liver, adrenal); (b) those...

...be responsible for activation of the MDR1 gene. Transient expression of MDR1 promoter fragments fused to a reporter gene such as that encoding chloramphenicol acetyl *transferase* (CAT) allowed the demonstration that both wild-type Harvey ras and mutant forms of p53 can activate the MDR1 promoter (51). The p53 responsiveness can...

...weight of 120,000-140,000 (98, 186). Processing to the mature form occurs with a half-life time $t_{1/2} = 1-2$ h in *human* cells or $t_{1/2} = 20-30$ min in *mouse* cells, and is *inhibited* by *tunicamycin* *treatment* (98, 186). All oligosaccharide side chains in *human* P-gp appear to be N-linked and can be removed with endoglycosidase F (186). Endoglycosidase F *treatment* converts mature P-gp to a lower-molecular-weight form that is similar to precursor protein (30, 186). In contrast, no shift in molecular weight results from neuraminidase-, endoglycosidase H-, or O-glycanase-*treatment* of *human* P-gp (30, 186). While 14C-labelled N-acetylglucosamine and galactose are efficiently incorporated into *human* P-gp, labelling with 14C-labelled fucose and mannose is poor (186). For none of the mammalian P-gps, however, has the exact composition of...

...the primary structure of mammalian P-gps (44, 68, 72, 100, 218, 242). The number and exact positions of the predicted glycosylation sites differ among *human* and rodent P-gps, but they are all located in the first putative extracellular loop, a region that is otherwise highly divergent in primary amino...

...gained from molecular genetic or biochemical studies in intact mammalian cells (202; SV Ambudkar, unpublished data). Site-directed mutagenesis and deletion analyses have confirmed that *human* P-gp contains three N-linked glycosylation sites, which are present in the amino-terminal half in the first extracytoplasmic loop (202).

Both cell biological and molecular genetic studies have indicated that the multidrug transport function of P-gp does not depend on glycosylation. Recombinant *human* P-gp expressed in MDR1-transfected murine cells has a lower apparent molecular weight than native *human* P-gp owing to altered glycosylation, but its multidrug transporter activity is not affected (SV Ambudkar, UA Germann, I Pastan, MM Gottesman, unpublished data). Recombinant...

...also reported that multidrug-resistant sublines can be isolated from lectin-resistant mutants, which are partially glycosylation-defective (136). Moreover, blocking N-linked glycosylation by *treatment* of multidrug-resistant cell lines with *tunicamycin* does not affect their drug resistance, providing even stronger evidence that glycosylation is not required for the drug efflux activity of P-gp (18, 120).

The most conclusive work on glycosylation involved a series of *human* P-gp mutants that lack N-linked glycosylation sites in the first extracytoplasmic loop (202). The analysis of selected transfectants revealed that these glycosylation-defective...

...route to or within the plasma membranes (202). Generally, P-gps are extremely stable proteins with a half-life of 48-72 h for the *human* and approximately 18 h for the *mouse* isoforms (53, 141, 186). Although *mouse* P-gp isoforms differ in their sites and state of glycosylation, the rate of degradation is similar among different *mouse* isoforms (53), which may be used as an argument against a role of glycosylation in stabilizing the membrane-associated polypeptide chain against proteolytic digestion. A ...of P-gp.

PHOSPHORYLATION

Phosphorylation has been established as a characteristic of mature P-gp in intrinsically drug-resistant or drug-selected cell lines of *human* and rodent origin (e.g. 16, 34, 80, 107, 145, 154, 186, 193, 210, 252). Recombinant *mdr* gene products expressed in mammalian or insect cells...

...kinase C (PKC) (e.g. 11, 12, 33, 75, 107, 152, 153, 171, 174, 179, 180). Through use of plasma membranes isolated from multidrug-resistant *human* KB-V1 cells, partially purified P-gp, or a synthetic *human* P-gp peptide, it was shown that the *human* MDR1 gene product is a target for *in vitro* phosphorylation by PKC, supporting the notion that PKC may serve as an important modulator in the...

...TPA), phosphorylation of P-gp is enhanced, drug accumulation reduced, and drug resistance increased (e.g. 1, 16, 34, 36, 75, 107). Conversely, protein kinase *inhibitors* (e.g. staurosporine, calphostin C) were found to decrease phosphorylation of P-gp and increase drug accumulation (e.g. 17, 39, 145). With few exceptions...

...state of phosphorylation of P-gp may regulate its drug efflux activity and, as a consequence, modulate multidrug resistance.

Unfortunately, many of the activators and *inhibitors* of protein kinases used to alter the state of phosphorylation of P-gp are not very specific and often cause multiple cellular effects, which makes...
...complicating side effects of protein kinase agonists and/or antagonists in multidrug-resistant cells have been defined to date.

1. Various protein kinase activators and *inhibitors* may affect P-gp expression, suggesting that protein kinase signal transduction pathways may regulate MDR1 gene expression. For example, the PKC activators TPA and diacyl...

...translational level, and this effect could be suppressed with staurosporine (41). Transcriptional activation of the MDR1 gene was shown to be attenuated by the PKC *inhibitor* H7 (236), while the PKA *inhibitor* H-87 was found to diminish MDR1 gene transcription (128). Staurosporine was observed to have dual (opposite) effects on levels of P-gp and/or and, therefore, *inhibit* its drug transport activity. For example, staurosporine and its derivatives have been shown to reverse multidrug resistance independent of their protein kinase *inhibitory* activities, presumably by interacting with P-gp directly (163, 201, 247). Similarly, calphostin C and certain isoquinolinesulfonamide (H7) derivatives may increase drug accumulation in multidrug...

...of actual sites of phosphorylation within P-gp to provide a basis for molecular genetic approaches involving site-directed mutagenesis. Phosphoamino acid analyses revealed that *human* P-gp contains phosphoserine exclusively (33, 107). A two-dimensional tryptic phosphopeptide map of *human* P-gp, obtained after metabolic labelling of multidrug-resistant cells with ³²P-orthophosphate, indicated the presence of at least three major phosphopeptides (39). The same two-dimensional map of tryptic phosphopeptides was obtained from *human* P-gp phosphorylated by PCK in vitro (38). Amino acid sequence analysis of the isolated tryptic phosphopeptides identified serine 661, serine 671, and one or more of serine 667, serine 675, or serine 683 as sites of phosphorylation in *human* P-gp (38) (see also Figure 1). Using a synthetic peptide encompassing amino acid residues 656-689, serine 667 was demonstrated to be a third PKC phosphorylation site in *human* P-gp (37). Similarly, serine 667, serine 671, and serine 683 were shown to be phosphorylated by PKA in vitro (37). Experiments with a different...

...associated protein kinase isolated from multidrug-resistant KB-V1 cells (V-1 kinase) confirmed serine 661 and serine 667 as major sites of phosphorylation in *human* P-gp (SV Ambudkar, TC Chambers, I Pastan, MM Gottesman, unpublished data). Moreover, a molecular genetic analysis of glutathione-S-*transferase* (GST) fusion proteins containing amino acid residues 644-689 of the *human* MDR1 gene product helped to corroborate these biochemical findings (35). A systematic mutational analysis was performed in which the biochemically identified phosphorylatable serine residues were...

...for phosphorylation by multiple kinases, despite the presence of numerous (>40) consensus sites for PKC and/or PKA phosphorylation distributed throughout the primary structure of *human* P-gp. These clustered phosphorylation sites are confined to a central cytosolic segment of approximately 60 amino acids that connects the two homologous halves of ...

...that this central cytosolic segment of P-gp may be more accessible to soluble enzymes than are other parts of the transporter.

Analyses of the *mouse* mdrlb P-gp corroborated that the linker region represents the preferred target for multisite phosphorylation of mdrl gene products by several kinases (173). Two serine residues are phosphorylated

in the *mouse* mdr1b gene product, namely serine 669 by PKC (analogous to serine 671 in *human* P-gp), and serine 681 by PKA (analogous to serine 683 in *human* P-gp) (173). Consensus sites of phosphorylation by PKC and/or PKA are also predicted in the linker region of other mammalian P-gps (e.g. the *mouse* mdr1a and the hamster pgp1 and pgp2 P-glycoproteins). Although the actual sites of phosphorylation have not been reported for most mdr gene products, it...

...drug transport activity (38).

The identification of the major sites of phosphorylation in P-gp provided an opportunity to introduce site-specific mutations within a *human* MDR1 cDNA and to assess their effects on the multidrug transport function. In a recent mutational analysis, five putative phosphorylation sites within the linker region of *human* P-gp (serines at positions 661, 667, 671, 675, and 683) were substituted either with nonphosphorylatable alanine residues (5A-mutant) or with aspartic acid residues detectable levels of phosphorylation in vivo and in vitro. This analysis reconfirmed that the major phosphorylation sites are confined to the linker region of *human* P-gp. Moreover, these data suggest that phosphorylation/dephosphorylation mechanisms do not play an essential role in the establishment of multidrug resistance mediated by *human* P-gp. Apparently, phosphorylation of P-gp is not necessarily required for its basal multidrug transporter activity. These experiments do not completely rule out that...

...drugs, but significant for the transport of a putative substrate(s) that still remain(s) to be identified. A recent study suggests that phosphorylation of *human* P-gp may indirectly regulate an endogenous chloride channel and that P-gp itself may not, as previously hypothesized, possess intrinsic channel activity (111).

MECHANISMS...

...resulted from gene amplification, was then exploited by a variety of molecular biological approaches to identify and clone specific mammalian multidrug-resistance genes operative in *human* cancers.

To establish MDR cell lines, cultured cells were selected for resistance to a specific anticancer drug. These drug selections were conducted in either a...

...resistance (mdr) locus and have led to a physical map spanning approximately 1 megabase (Mb) of the native mdr genomic region in both rodent and *human* MDR cell lines.

MOLECULAR CYTOGENETICS OF IN VITRO MDR MODEL SYSTEMS

An obvious feature of many of the independently selected multidrug-resistant cell lines was...an unknown gene in several of the MDR cell lines to facilitate its cloning and the subsequent identification of specific mdr genes in rodents and *humans* (104, 189, 192, 211).

ISOLATION OF AMPLIFIED GENE SEQUENCES IN MDR CELLS

Two of the cloning strategies employed to isolate novel mdr genes were based...

...protocol and shown to detect overexpressed mRNAs in an MDR hamster cell line (191), this sequence was used as a DNA probe to isolate amplified *human* genomic fragments from colchicine-selected MDR KB cells (78, 192), and to identify amplified MDR genomic DNA sequences and cDNAs in MDR murine cell lines...

...during drug selections occurred concomitantly with increased expression

of *mdr* genes. The P-gp RNA transcript is approximately 4.5 kb in size in both *human* (217) and rodent (66, 101, 231) MDR cell lines.

Human MDR genomic DNAs have also been sequenced to locate positions of introns within the two halves of the P-gp molecule (45). The *human* MDR1 gene contains 28 exons, interspersed with introns that together extend over greater than 100 kb of genomic DNA. A comparison of the positions of ...

...profiles have been explained, in part, by the identification of two multidrug-resistance genes, each conferring different, but overlapping, profiles of MDR (68). However, in *human* MDR cells, where there is only one MDR1 gene, MDR profile differences among different MDR cell lines are largely unexplained. Although spontaneously occurring basepair mutations have been shown to alter the MDR profile of *human* cell lines (see above), the generation of basepair mutations during drug selections does not appear to be common. For example, the preferential adriamycin resistance of the *human* cell line KB-A1 (216) does not appear to be due to the presence of basepair mutations in the amplified MDR1 genes of this cell...

...mutations in the amplified copies of the MDR1 gene. Thus, other mechanisms, either genetic or epigenetic, appear to result in the different MDR profiles of *human* MDR1-expressing cell lines.

Several hypotheses have been offered to explain MDR profile differences among MDR cell lines. First, ...may be operative within single MDR cells, presents a great challenge to the clinician, who must consider concurrent strategies aimed at different MDR mechanisms in *human* cancers.

A third possibility is that genes that are expressed as a result of their co-amplification with MDR genes may contribute to the different...

...amplified with the *mdr* genes, and their expression contributes to some of the protein changes that have been documented in MDR cells. For example, in *human* MDR KB cells that were selected independently in three different drugs (adriamycin, vinblastine, and colchicine), two-dimensional gel analysis identified a number of differential protein...

...a 21-kDa protein, in only the colchicine-selected cells (185, 216). The 21-kDa protein has since been identified as a calcium-binding protein in *human* MDR cells that is homologous to the Sorcin protein also overexpressed in MDR rodent cells (155). Recent studies have shown that the overexpression of the...

...results from overexpression of its cognate gene, termed CP22, which lies on multigene circular DNA amplicons and is linked to the native *mdr* locus in *humans* (207) (PV Schoenlein, Y Sugimoto, T Tsuruo, I Pastan, MM Gottesman, unpublished data), as the Sorcin gene has been shown to be linked to the *mdr* locus in rodents (241, 243). To date, no distinct pattern of drug resistance has been correlated to the amplification of the CP22 gene in *human* MDR cell lines, its sorcin gene homolog in murine cell lines, or any of the other genes that differentially co-amplify with the *mdr* genes during drug selections (described in detail in the next section). Thus, the role, if any, of the genes that are co-amplified with the *human* MDR1 genes will only be conclusively shown by cotransfection experiments in which their cDNAs and the MDR1 cDNA are introduced in various combinations into drug...

...locus (207, 225, 241, 243). Studies that have identified the specific, but differential amplification and expression patterns of these linked genes in many rodent and *human* MDR cell lines have led to a more complete understanding of the structural and genetic organization of the rodent and *human* *mdr* locus, the genetics of multidrug resistance, and gene amplification mechanisms in mammalian cells (reviewed in 205). Non-*mdr* cDNAs representing amplified genes that are...

...cDNAs were sufficiently conserved to allow their use in the analysis of gene amplification structures and the corresponding genomic DNA regions in MDR cells from *mouse* (224) and *human* (240). Taken together, these physical mapping studies provided strong evidence that gene classes 2-6 are syntenic in both rodents and *humans*, suggesting a similar overall structure of the *human* and rodent *mdr* (PGY) locus.

The main conclusion from studies analyzing the multigene amplification structures in MDR cell lines expressing P-gp is that only rodent cells resulting from expression of co-amplified non-*mdr* genes, because the two *mdr* genes (designated *mdr1a* and *mdr1b* in *mouse* and *pgp1* and *pgp2* in hamster), which have been shown to encode distinct MDR profiles in *mouse* cells (68), are also differentially co-amplified upon drug selection (66, 122), although apparently not in direct response to the specific drug used for selection...

...differentially co-amplified and expressed in MDR cell lines, but it does not appear to confer an MDR phenotype (203).

In studies conducted in the *human* MDR KB cell lines that were selected in either colchicine, vinblastine, or adriamycin (4, 216), large multigene circular DNA amplicons have been identified (206) (described...

...further, more direct studies are needed before we can exclude a role for differentially co-amplified non-*mdr* genes in the final MDR profile of *human* cells.

PFGE techniques (208) were used to identify and determine the approximate size of extrachromosomal circular DNA amplicons in the MDR KB cell lines (Figure...

...JT Barrett, unpublished data). Recent hybridization studies have determined that the 890-kb episome in the KB-C1 cell line contains the *MDR2* gene; the *human* *sorcin* gene, designated CP22; and at least two other genes of unknown function (PV Schoenlein, Y Sugimoto, T Tsuruo, I Pastan, MM Gottesman, unpublished data). The order of these genes is schematically shown in Figure 4, both in the 890-kb amplicon and at the *human* native MDR locus. These mapping studies are consistent with earlier PFGE studies by Roninson and colleagues, which demonstrated the location of the *MDR1* and *MDR2*...

...by *NotI* and *NruI* restriction digests (Figure 4), it can be inferred that the genes represented by the c3, c5, and CP22 cDNAs map to *human* chromosome 7, band q21.1, where the *MDR1* and *MDR2* genes have been previously localized (31, 76).

TRANSGENIC APPROACHES TO MANIPULATE EXPRESSION OF P-GLYCOPROTEIN IN INTACT *ANIMALS*

Many of the hypotheses concerning the physiologic function of the P-glycoproteins were based on correlative studies in tissue culture systems. To demonstrate definitively that...

...the *MDR1* gene was responsible for resistance of cells to anticancer drugs in vivo and to determine the physiological function of P-gp in intact *animals*, it was necessary to introduce *MDR1* genes into transgenic mice and to ablate endogenous *mdr* genes to create P-gp "knockout" mice. Both of these...

...the original hypotheses concerning the function of *mdr1* genes and yielded new, unexpected information about the function of the closely related *mdr2* gene in the *mouse*.

The introduction of a *human* *MDR1* cDNA under control of a chicken *b-actin* promoter into the genome resulted, unexpectedly but

serendipitously, in one strain in which the gene was expressed in bone marrow cells (79). This expression resulted in resistance of these *animals*, and of *animals* receiving bone marrow transplants from the MDR1 transgenic mice, to leukopenia induced by a variety of cytotoxic anticancer drugs (79, 157-159). These results demonstrate that levels of expression of the MDR1 gene found in *human* cancers and in normal *human* tissues are sufficient to confer multidrug resistance in vivo, and raise the possibility that introduction of a *human* MDR1 gene into the bone marrow of patients might protect their bone marrow against the cytotoxic effects of chemotherapy (see section on GENE THERAPY USING...

...to high levels in the brain of mdrla-defective mice. In addition, increased plasma levels of vinblastine due to reduced excretion were found in these *animals* after intravenous administration of this ...of such cells in the presence of cytotoxic drugs that are P-gp substrates (158). Through use of a retroviral expression vector in which the *human* MDR1 cDNA was under control of a Harvey sarcoma virus long terminal repeat (LTR) (175), it was possible to show that transduction of *mouse* bone marrow cells (150) and *mouse* erythroleukemia cells (67) resulted in resistance in vitro to cytotoxic drugs. When *mouse* bone marrow transduced with these MDR1 retroviruses was transplanted into mice, expression of MDR1 mRNA and P-gp was detected on circulating peripheral blood cells, and *treatment* of mice with taxol enriched these MDR1-transduced cells in the peripheral blood (178, 222). The finding of single unique sites of integration of the...

...transplanted and still be resistant to cytotoxic drugs in their new hosts (109), suggested that the MDR1 retrovirus was integrating into multipotential stem cells. Isolated *mouse* stem cells expanded ex vivo can also be efficiently transduced with MDR1 retroviruses and transplanted into mice (135). These MDR1 retroviruses are also able to transduce *human* bone marrow CD34 positive cells (a population that includes bone marrow stem cells) with efficiencies of up to 20[percent] (110, 250). These studies provided...

...to patients with cancer. In addition, MDR1 vectors can be engineered to carry a passenger gene. If the transfected cells are in the bone marrow, *treatment* of *animals* with MDR drugs will have two effects. One is that the drugs kill untransduced cells, creating space in the bone marrow for the transduced cells...cells inadvertently transduced to drug resistance, such as cancer cells or other inappropriate cell types.

The future use of selectable markers, such as MDR1, in *human* gene therapy depends on developing solutions to several problems. The safest and most efficient gene delivery systems should be utilized. It is unclear at present...

...Genetic studies on the multidrug transporter have come full cycle. A genetic mechanism that protects cancer cells from chemotherapy is about to be exploited for *treatment* of cancer and inborn errors of metabolism.

Added material

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Figure 1 Schematic diagram showing a hypothetical model of *human* P-glycoprotein with 12 transmembrane domains and two ATP sites. In this diagram, each circle represents an amino acid residue, with filled-in circles showing...baculovirus expression system. Biochemistry 33:10313-18

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New mechanisms of drug resistance in parasitic protozoa.

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ABSTRACT: The main line of defense now available against parasitic protozoa--which are responsible for major diseases of *humans* and domestic *animals*--is chemotherapy. This defense is being eroded by drug resistance and, with few new drugs in the pipeline, prevention and circumvention of resistance are medical...

...and cancer cells, the tools to tackle this problem are rapidly improving. Transformation with exogenous DNA is now possible with all major parasitic protozoa of *humans*. Hence, putative resistance genes can be tested in sensitive protozoa, allowing an unambiguous reconstruction of resistance mechanisms. Gene cloning, the polymerase chain reaction, and monoclonal...

TEXT:

... now available, progress should be rapid in the coming years.

INTRODUCTION

Parasitic protozoa are responsible for some of the most devastating and prevalent diseases of *humans* and domestic *animals*. Malaria (*Plasmodium* spp.), the various forms of (muco)cutaneous and visceral leishmaniasis (*Leishmania* spp.), African sleeping sickness (*Trypanosoma brucei gambiense*, *Trypanosoma brucei rhodesiense*), South-American Chagas' disease (*Trypanosoma cruzi*), amoebic dysentery (*Entamoeba* spp.), and toxoplasmosis (*Toxoplasma* spp.) are serious diseases that threaten the lives of nearly one quarter of the *human* population worldwide. In addition, the

parasitic diseases caused by *Trichomonas vaginalis* (vaginitis, urethritis) and *Giardia duodenalis* (diarrhea) are very widespread and unpleasant, even though not life-threatening. Protozoal parasites also result in enormous losses of life and productivity of domesticated *animals*, both mammals and fowl.

Drugs and prevention are the two major weapons now available against protozoan parasites. There are high hopes that effective vaccines may... leave a large window for the development of parasite-specific drugs. It is not always appreciated that the protozoal parasite differs much more from a *human* cell than from cells of fungi or plants. On an evolutionary scale deduced from differences in small-subunit ribosomal RNAs (58, 167), protozoa such as *Giardia lamblia* and *Trypanosoma brucei* are nearly as similar to *Escherichia coli* as to *humans*. Hence, it is not surprising that fairly effective drugs are available for many parasitic diseases. It is even embarrassing that there are still major parasites...RELATED TRAFFIC ATPASES

MAMMALIAN P-GLYCOPROTEINS

The importance of P-glycoproteins (Pgps) and related transmembrane transporters for drug resistance in organisms ranging from bacteria to *human* tumor cells has been amply demonstrated since this class of proteins was discovered by Juliano & Ling (96) in multidrug-resistant hamster tumor cells. Pgps belong...by lowering the intracellular drug concentration by drug extrusion (195). MRP is not just another member of the Pgp family, however. The sequence identity between *human* MDR 1 Pgp and MRP is only 23[percent], and MRP seems to have a more asymmetric structure than Pgp (34). Recent experiments indicate that...

...drug with GSH is a complex affair (89, 124). It requires not only the ability to conjugate the drug (e.g. by a GSH-S-*transferase*), but also the ability to maintain high levels of GSH and the ability to export the GSH-drug conjugate out of the cell at a...

...continuing influx of drug into the cell. The resistance obtained therefore depends on the activity of at least three enzyme systems: GSH biosynthesis, GSH-S-*transferase*, and the GS-X pump.

P-GLYCOPROTEINS AND RELATED TRANSPORT PROTEINS IN PARASITES

Table 1 shows that Pgps and other related putative transporters are widely ...

...by the mammalian MDR1-type Pgps is the Pgp encoded by the *ldmdr1* gene of *Leishmania donovani* (82, 83). These drugs are not used to *treat* leishmaniasis, but *Leishmania* spp. may encounter toxic natural products in other stages of its life cycle. The other individual Pgps of parasitic protozoa are discussed in the relevant sections.

RESISTANCE TO CHLOROQUINE, MEFLOROQUINE, QUININE, AND HALOFANTRINE

Chloroquine is the drug of choice for *treating* malaria. The emergence of *Plasmodium falciparum* that is resistant to chloroquine in the late 1950s in Southern Asia and South America has been a major...

...the parasite (166). This polymerase is thought to be essential for the polymerization of ferriprotoporphyrin IX into the malaria pigment of infected erythrocytes, and its *inhibition* results in the accumulation of toxic heme degradation products, proposed to cause the death of the parasite (61). Other targets remain under investigation, however. For...

...104) reported that chloroquine efflux is increased in resistant parasites, and Martin et al (120) reported that verapamil, the classical agent to reverse MDR in *animal* cells, is able to restore chloroquine

sensitivity to resistant cells. Subsequently, several other agents that reverse MDR were shown to reverse chloroquine resistance as well...

...Pgh1 Pgp encoded by pfmdr1 was proposed to be the efflux pump that caused increased efflux of chloroquine from the parasite, and this pump was *inhibited* by verapamil (65). This simple picture seemed to be supported by the preferential association of chloroquine resistance with specific alleles of pfmdr1 (64). It came...designed specifically for chemotherapy. Oxyanions in the form of aromatic arsenicals or drugs containing the related metal antimony are still first-line drugs in the *treatment* of trypanosomiasis and leishmaniasis.

RESISTANCE TO ARSENICALS IN TRYPANOSOMES

Trypanosoma brucei, a fly-transmitted parasite, is responsible for sleeping sickness in *humans*. Melamine-based arsenicals such as melarsoprol (MelB), diamidines such as pentamidine, and a few other drugs are used to *treat* *human* sleeping sickness, but melarsoprol is the mainstay for *treatment* of the most advanced cases affecting the central nervous system (8). Resistance to melarsoprol and other arsenical drugs has been encountered both in Trypanosoma species...

...arsenicals is due to loss of uptake (29).

RESISTANCE TO OXYANIONS IN LEISHMANIA SPP.

Leishmania spp. are distributed worldwide, with 400,000 new cases of *human* leishmaniasis each year (6). The clinical manifestations vary, depending on the Leishmania spp., from self-healing cutaneous lesions to visceral infections that are usually fatal if left untreated. The *treatment* of choice for all forms of leishmaniasis is the administration of the pentavalent antimonial-containing drugs (129). The mode of action of antimonials in Leishmania...X pump. Although the As(SG)3 complex can form spontaneously, there is circumstantial evidence that complex formation may be accelerated by a glutathione-S-*transferase* (GST). The GS-X pump appeared identical to MRP, the MDR-associated protein. In the ABC transporter family, MRP is most closely related to PgpA...

...113) and, more importantly, for the unexpected observation of Callahan et al (28) that transfection of the pgpA gene into L. major results in an *inhibition* of the energy-dependent influx of a trivalent antimonial without any measurable effect on efflux. The authors suggest "that overexpression of PgpA confers a dominant...

...catalyzes the reduction of dihydrofolate to tetrahydrofolate, is an important target for chemotherapy. The anti-DHFR drugs are termed antifolates and are used in the *treatment* of parasitic infections caused by Plasmodium falciparum and Toxoplasma gondii in *humans*. DHFR *inhibitors* used in the *treatment* of microbial diseases are often combined with sulfonamides. Sulfonamides are *inhibitors* of the enzyme dihydropteroate synthase (DHPS), and *inhibition* of this enzyme blocks the de novo synthesis of dihydrofolates. Antifolates and sulfonamides act synergistically to deplete the pool of reduced folates and eventually ... 63, 164). Several of these mutations may coexist in the same cell.

MUTATIONS IN DHFR AND DHPS

Pyrimethamine and cycloguanil are two antifolates used to *treat* malaria. Pyrimethamine resistance in P. falciparum can arise through several mechanisms. The most commonly found is a single point mutation in the DHFR at position...

...a serine to an asparagine (38, 148). These parasites are not

cross-resistant to cycloguanil. This mutation is also found in field isolates refractory to *treatment* (146), but in cell lines selected in vitro, other DHFR amino acid residues, in addition to position 108, were altered, and these mutations may confer...

...such amplicons when the preferred mechanism of resistance is unavailable.

TRANSPORT MUTATIONS IN LEISHMANIA SPP.

Although none of the currently available antifolates is suitable for *treatment* of leishmaniasis in patients, much experimental work has been done on folate metabolism and resistance to antifolates in *Leishmania* spp. cultured in the laboratory. *Leishmania*...ability to grow on biopterin-supplemented folate-deficient medium (141).

Purified LTDH/PTR1 exhibits an NADPH-dependent reductase activity, reduces biopterin and folate, and is *inhibited* by methotrexate. Activity is greater for the most oxidized form of the two classes of substrate, and biopterin is a much better substrate than folate...

...*Leishmania* spp. As pointed out earlier (14, 141), the novelty and possible uniqueness of the LTDH/PTR1 pathway should make it possible to develop specific *inhibitors* of this enzyme. As *inhibitors* of the mammalian DHFR are being developed (156), lead compounds could already be available. LTDH/PTR1 *inhibitors*, in particular in combination with DHFR-TS *inhibitors* (see Figure 2), might be highly effective in the *treatment* of leishmaniasis.

MISCELLANEOUS RECENTLY DESCRIBED MECHANISMS OF DRUG RESISTANCE RESISTANCE TO PURINE ANALOGUES

All parasitic protozoa so far studied are auxotrophic for purines, whereas the mammalian cells that they infect are capable of de novo purine synthesis. This clear biochemical difference suggests that purine analogues could be used successfully to *treat* parasitic disease, and indeed several pyrazolopyrimidine analogues of hypoxanthine and inosine were shown to be toxic to pathogenic parasites (119). The potential for a rational...

...*Trypanosoma cruzi* (2, 3) has been extensively studied. The purine

analogue allopurinol binds to purified HGPRT, and allopurinol was reported to be useful in the *treatment* of American leishmaniasis (121), although others are less enthusiastic about allopurinol efficacy (129). Recently Pfefferkorn & Borotz (151) mutagenized *Toxoplasma gondii* and selected a clone resistant...

...of nucleoside base extrusion or, more likely, result from a dominant-negative effect on the transporters involved in uptake.

Mycophenolic acid (MPA) is an effective *inhibitor* of inosinemonophosphate (IMP) dehydrogenase, an essential enzyme for de novo synthesis of guanine nucleotides. MPA is too toxic for clinical use, but it is used...

...laboratory, and interesting resistant mutants have been obtained in several protozoa. As *Leishmania* spp. readily counteract metabolic blocks by amplifying the gene for the enzyme *inhibited*, it is not surprising that a mutant of *L. donovani*, 100-fold resistant to MPA, proved to have a ...efficiently (80).

RESISTANCE TO METRONIDAZOLE

Metronidazole has been used for more than 30 years against anaerobic bacteria and protozoa and is the first choice for *treatment* of three of the most prevalent *human* parasites, *Trichomonas vaginalis*, *Giardia duodenalis*, and *Entamoeba histolytica*. The toxicity of metronidazole and related nitroimidazoles depends on the presence of an electron donor of low ...

...Clearly, a transformation assay for parasitic organisms affected by metronidazole is required to prove unambiguously the resistance mechanisms proposed thus far.

RESISTANCE TO ORNITHINE DECARBOXYLASE *INHIBITORS*

Ornithine decarboxylase is the enzyme catalyzing the conversion of ornithine into the polyamine putrescine. The further conversion of putrescine into spermidine requires S-adenosylmethionine. The conjugation of spermidine and GSH in trypanosomatids results in the formation of trypanothione. A specific *inhibitor* of ornithine decarboxylase, DL- α -difluoromethylornithine (DFMO, eflornithine) was developed as an antitumor agent, but was also found to be highly effective as an antitrypanosomal...

...Bacchi et al (9). The most distinctive metabolic alterations in these isolates were related to S-adenosylmethionine (AdoMet) metabolism. Whereas sensitive cells reacted to the *inhibition* of ornithine decarboxylase with up to a 100-fold increase in AdoMet, the resistant strains showed a more moderate elevation, which correlated with a decrease...

...on trypanocidal agents suggests interesting new possibilities for the use of drug combinations. If trypanothione is indeed the main target of arsenicals, DFMO as an *inhibitor* of trypanothione synthesis should sensitize trypanosomes to arsenicals. Such sensitization has indeed been observed in a *mouse* model (10). A new AdoMet decarboxylase *inhibitor*, the deoxyadenosine analogue MDL73811, is an even more effective *inhibitor* of polyamine synthesis than is DFMO (8). MDL73811 enters trypanosomes via a purine transporter, but which one is not yet known. As melamine-based arsenicals...designed purine analogues that enter via other purine transporters.

RESISTANCE TO EMETINE

The plant alkaloid toxin emetine used to be the first-line drug for *treatment* of amebiasis caused by *E. histolytica*, and emetine is still sometimes used for this purpose. Samuelson et al (163) mutagenized *E. histolytica* and selected a...

...a drug than are wild-type cells (110). The parasites transfected with vectors containing antibiotic resistance genes are resistant to drugs not commonly used to *treat* patients. *Leishmania* spp. cells expressing the neomycin phosphotransferase gene and resistant to the selective drug G418, however, were cross-resistant to paromomycin, a drug now used in the *treatment* of *Leishmania* spp. (76). The transfer of this marker gene to wild-type *Leishmania* spp. in the field is clearly undesirable.

OUTLOOK

Reviews on drug resistance tend to finish with a grand eulogy on the importance of this topic for *humanity* (and rightly so). We would like to end here by emphasizing that studies of drug resistance are also great fun. Parasite biochemistry is rarely straightforward...Watkins W, Sims P, Hyde J. 1995. Correlation of sulfadoxine resistance with point mutations located within the bifunctional hydroxymethyl-dihydrobiopterin pyrophosphokinase-dihydropteroyl synthase gene of the *human* malaria parasite *Plasmodium falciparum*. Mol. Biochem. Parasitol. In press

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6/3,K/31 (Item 1 from file: 103)
DIALOG(R)File 103:Energy SciTec
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04361434 AIX-29-062628; EDB-98-121849

**Title: The leukocyte common antigen (CD45) on *human* pre-B leukemia cells:
variant glycoprotein form expression during the cell exposure to
phorbol ester is blocked by a nonselective protein kinase *inhibitor*
H7**

Author(s): Duraj, J.; Sedlak, J.; Chorvath, B. (Department of Molecular Immunology, Cancer Research Institute, Slovak Academy of Sciences, 812 32 Bratislava (Slovak Republic)); Rauko, P. (Department of Experimental Tumor Therapy, Cancer Research Institute, Slovak Academy of Sciences, Bratislava (Slovak Republic))

Source: Neoplasma v 44:3. Coden: NEOLA4 ISSN: 0028-2685

Publication Date: 1997

p 205-211

Contract Number (Non-DOE): GA-VEGA-95/5305/353 and GA-VEGA-2/1335/96

Language: English

**Title: The leukocyte common antigen (CD45) on *human* pre-B leukemia cells:
variant glycoprotein form expression during the cell exposure to
phorbol ester is blocked by a nonselective protein kinase *inhibitor*
H7**

Abstract: The *human* pre-B acute lymphoblastic leukemia cell line REH6 was utilized for characterization of CD45 glycoprotein by monoclonal antibodies (mAb) recognizing four distinct CD45 antigen specificities
...

...0-7.5. Nonrestricted CD45 epitopes were not affected by the sialyl acid cleavage with sodium meta-periodate or neuraminidase, but were sensitive to both, *tunicamycin*, the N-glycosylation *inhibitor* and monensin, an *inhibitor* of protein transport through the Golgi compartment. O-sialoglycoprotein endopeptidase from Pasteurella haemolytica A1 partially cleaved CD45RA and CD45RB epitopes, while nonrestricted CD45 determinants were...

...affected by this enzyme. Limited proteolysis of this antigen resulted in the appearance of 160-180 kDa peptide domains which retained CD45 epitopes. Further, the *treatment* of cells with phorbol myristate acetate (PMA) induced marked down-regulation of 220 and 190 kDa isoforms and the appearance of new 210, 180 and...

...found on parental cells. This PMA effect was not accompanied by the programmed cell death and was markedly blocked by a nonselective

protein kinase (PK) *inhibitor* iso-quinoline sulfonamide H7.
Modulation of CD45 by phorbol esters might serve as an in vitro model
for an additional insight into the function of...
...Descriptors: ENZYME *INHIBITORS*;
Broader Terms: *ANIMAL* CELLS...

...PHOSPHORUS-GROUP *TRANSFERASES*; ...

...*TRANSFERASES*;

6/3,K/32 (Item 2 from file: 103)
DIALOG(R)File 103:Energy SciTec
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01878668 INS-86-039293; EDB-87-006301
**Title: *Tunicamycin*-induced *inhibition* of a glycolipid:GalNAc-
transferase in guinea pig tumor cells**
Author(s): Das, K.K.; Basu, M.; Basu, S.
Affiliation: Univ. of Notre Dame, IN
Conference Title: 76. annual meeting of the Federation of American Society
for Experimental Biology
Conference Location: Washington, DC, USA Conference Date: 8 Jun 1986
Source: Fed. Proc., Fed. Am. Soc. Exp. Biol. (United States) v 45:6.
Codon: FEPR
Publication Date: May 1986
p 1821
Report Number(s): CONF-8606151-
Language: English

**Title: *Tunicamycin*-induced *inhibition* of a glycolipid:GalNAc-
transferase in guinea pig tumor cells**
...Abstract: tumor cells are of the present interest. Recently, the authors
established the biosynthesis in vitro of GbOse4Cer and GbOse5Cer from
GbOse3Cer by two different GalNAc-*transferases* (GalNAcT-2 and
GalNAcT-3) isolated from chemically transformed guinea pig tumor cells
(104Cl and 106B). When these cells were incubated in the presence of
tunicamycin (0.2-2 ..mu..g/ml), the activity of GalNAcT-2
(UDP-GalNAc:GbOse3Cer(..beta..1-3)GalNAcT) was *inhibited* (90%),
whereas GalT-4 (UDP-Gal:LcOse3Cer(..beta..1-4)GalT) and GalT-5
(UDP-Gal:LcOse5Cer(..cap alpha..1-3)GalT) remained unchanged. The
effect of *tunicamycin* was minimal within 6 hrs of *treatment*.
However, 50% and 75% *inhibition* was observed after *treatment* of
these cells for 12 and 24 hr, respectively. The *inhibitory* effect of
tunicamycin on GalNAcT-2 can be reversed after 12-24 hr of its
removal from the medium. The incorporation of (/sup 3/H)-leucine in
total protein remained unchanged during *tunicamycin* *treatment*. The
inhibition of glycoproteins was further confirmed by the *inhibition*
(95%) of (2-/sup 3/H)Man incorporation in the acid precipitable
material. When cells were grown in the presence of insulin, the
GalNAcT-2...
...Major Descriptors: GLYCOLIPIDS -- *INHIBITION*; **TRANSFERASES* --
ENZYME ACTIVITY
...Broader Terms: *ANIMAL* CELLS...
...*ANIMALS*;

6/3,K/33 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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17352828 PASCAL No.: 05-0429136

NGF-induced phosphatidylinositol 3-kinase signaling pathway prevents thapsigargin-triggered ER stress-mediated apoptosis in PC12 cells

SHIMOKE Koji; KISHI Soichiro; UTSUMI Takahiro; SHIMAMURA Yuichi; SASAYA Harue; OIKAWA Tadao; UESATO Shinichi; IKEUCHI Toshihiko

Faculty of Engineering and High Technology Research Center (HRC), Kansai University, 3-3-35 Yamate-cho, Suita, Osaka 564-8680, Japan

Journal: Neuroscience letters, 2005, 389 (3) 124-128

Language: English

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Tunicamycin, an ***inhibitor*** of the glycosylation of newly biosynthesized proteins, induces endoplasmic reticulum (ER) stress and subsequent apoptosis, and caspase family proteases are activated during the process of ER stress-mediated apoptosis. In the present study, we showed that thapsigargin (Th), an ***inhibitor*** of the sarcoplasmic/endoplasmic reticulum Ca SUP 2 SUP + ATPase (SERCA), also induced ER stress-mediated apoptosis, and nerve growth factor (NGF) prevented the apoptosis in PC12 cells. We also found that LY294002, an ***inhibitor*** of phosphatidylinositol 3-kinase (PI3-K), reduced the survival of cells ***treated*** with NGF for 24 h in the presence of Th. We discovered that the activities of caspase-3, -9 and -12 were increased time-dependently after the ***treatment*** with Th, and NGF suppressed the Th-triggered activation of caspase-3, -9 and -12. LY294002 diminished the effect of NGF on the inactivation of all these caspases. These results indicate that the NGF-induced PI3-K signaling pathway prevents Th-triggered ER stress-specific apoptosis via ***inhibition*** of caspase-mediated apoptotic signal.

English Descriptors: Nerve growth factor; 1-Phosphatidylinositol 3-kinase; Signal transduction; Stress; Apoptosis; In vitro; Neuron; Cell line; Caspase; Cysteine endopeptidases; ***Animal***

French Descriptors: Facteur croissance nerf; 1-Phosphatidylinositol 3-kinase; Transduction signal; Stress; Apoptose; In vitro; Neurone; Lignée cellulaire; Caspase; Cysteine endopeptidases; ***Animal***; Lignée PC12

Spanish Descriptors: Factor crecimiento nervio; 1-Phosphatidylinositol 3-kinase; Transduccion senal; Estres; Apoptosis; In vitro; Neurona; Linea celular; Caspase; Cysteine endopeptidases; ***Animal***

Broad Descriptors: ***Transferases***; Enzyme; Peptidases; Hydrolases; Cell death; Rat; Rodentia; Mammalia; Vertebrata; ***Transferases***; Enzyme; Peptidases; Hydrolases; Mort cellulaire; Rat; Rodentia; Mammalia; Vertebrata; ***Transferases***; Enzima; Peptidases; Hydrolases; Muerte celular; Rata; Rodentia; Mammalia; Vertebrata

6/3,K/34 (Item 2 from file: 144)

DIALOG(R)File 144:Pascal

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14818611 PASCAL No.: 00-0501158

Homocysteine-responsive ATF3 gene expression in *human* vascular endothelial cells : activation of c-Jun NH SUB 2 -terminal kinase and promoter response element

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Japanese Foundation for Cancer Research, Tokyo, Japan
Journal: Blood, 2000, 96 (6) 2140-2148
Language: English

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**Homocysteine-responsive ATF3 gene expression in *human* vascular
endothelial cells : activation of c-Jun NH SUB 2 -terminal kinase and
promoter response element**

... and functions as a stress-inducible transcriptional repressor. To understand the stress-induced gene regulation by homocysteine, we investigated activation of the ATF3 gene in *human* endothelial cells. Homocysteine caused a rapid induction of ATF3 at the transcriptional level. This induction was preceded by a rapid and sustained activation of c...

... homocysteine appeared to be specific, because cysteine or homocystine had no appreciable effect, but it was mimicked by dithiothreitol and beta-mercaptoethanol as well as *tunicamycin*. The homocysteine effect was not *inhibited* by an active oxygen scavenger. Deletion analysis of the 5' flanking sequence of the ATF3 gene promoter revealed that one of the major elements responsible...

... immunoprecipitation, and cotransfection assays demonstrated that a complex (or complexes) containing ATF2, c-Jun, and ATF3 increased binding to the ATFICRE site in the homocysteine-*treated* cells and activated the ATF3 gene expression, while ATF3 appeared to repress its own promoter. These data together suggested a novel pathway by which homocysteine...

English Descriptors: Endothelial cell; Biological activity; Transcription factor; Signal transduction; Gene; Gene expression; Protein kinase; *Human*; Homocystinuria; Pathophysiology; Thiol; Sulfur containing aminoacid; Transcription factor ATF

Broad Descriptors: *Transferases*; Enzyme; Metabolic diseases; Aminoacid disorder; Nervous system diseases; Central nervous system disease; Cerebral disorder; Genetic disease; Enzymopathy; *Transferases*; Enzyme; Metabolisme pathologie; Aminoacidopathie; Systeme nerveux pathologie; Systeme nerveux central pathologie; Encephale pathologie; Maladie hereditaire; Enzymopathie; *Transferases*; Enzima; Metabolismo patologia; Aminoacido alteracion; Sistema nervioso patologia; Sistema nervosio central patologia; Encefalo patologia; Enfermedad hereditaria; Enzimopatía

6/3,K/35 (Item 1 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

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10681833 PMID: 8067807

Leishmania gene amplification: a mechanism of drug resistance.

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Departamento de Genetica y Microbiologia, Facultad de Medicina, Universidad de Murcia, Spain.

Annals of tropical medicine and parasitology (ENGLAND) Apr 1994, 88

(2) p123-30, ISSN 0003-4983 Journal Code: 2985178R

Publishing Model Print

Document type: Journal Article; Review

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Leishmania spp. are excellent models for analysing the mechanisms of drug resistance, one of the major barriers to the *treatment* and control of several major diseases. They may become refractory to drugs as the result of gene amplification. Amplified Leishmania DNA are extrachromosomal, usually circular...

... G circles and ODC140-L minichromosomes are extrachromosomal amplifications encoding copies of dihydrofolate reductase-thymidylate synthase, glycosyltransferase, and ornithine decarboxylase, respectively, and conferring resistance to *inhibitors* of these gene products (methotrexate, *tunicamycin* and alpha-difluoromethylornithine, respectively). Another DNA amplification, named the H circle, has been detected in response to several unrelated drugs and confers drug resistance. Leishmania...

; *Animals*; DNA, Circular--genetics--GE; Eflornithine--pharmacology--PD; *Humans*; Leishmania--drug effects--DE; Tetrahydrofolate Dehydrogenase --genetics--GE; *Transferases* (Other Substituted Phosphate Groups) --genetics--GE

Enzyme No.: EC 1.5.1.3 (Tetrahydrofolate Dehydrogenase); EC 2.7.8 (*Transferases* (Other Substituted Phosphate Groups)); EC 2.7.8.15 (UDPacetylglucosamine-dolichyl-phosphate acetylglucosamine-1-phosphate *transferase*)

Chemical Name: DNA, Circular; DNA, Protozoan; Eflornithine; Tetrahydrofolate Dehydrogenase; *Transferases* (Other Substituted Phosphate Groups); UDPacetylglucosamine-dolichyl-phosphate acetylglucosamine-1-phosphate *transferase*

6/3,K/36 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10405789 PMID: 8280061

Effect of GTP on the dolichol pathway for protein glycosylation in rat liver microsomes.

Bossuyt X; Blanckaert N
Laboratory of Biological Chemistry, Katholieke Universiteit Leuven, Belgium.

Biochemical journal (ENGLAND) Dec 15 1993, 296 (Pt 3) p633-7, ISSN 0264-6021 Journal Code: 2984726R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

... indicating that GTP hydrolysis was crucial. Though dolichyl pyrophosphate NN'-diacetylchitobiose [Dol-PP-(GlcNAc)₂] was the main radiolabelled product formed upon incubation of GTP-*treated* microsomes with UDP-GlcNAc, GTP selectively stimulated UDP-GlcNAc:dolichyl phosphate (Dol-P) N-acetylglucosaminyl 1-phosphotransferase (N-acetylglucosaminyl 1-phosphotransferase). This conclusion was reached on the basis of experiments in which *tunicamycin* was used to selectively *inhibit* N-acetylglucosaminyl 1-phosphotransferase. The enhanced transformation of Dol-P to dolichyl pyrophosphate N-acetylglucosamine (Dol-PP-GlcNAc) by GTP ultimately led to enhanced protein...

; Acetylglucosamine--metabolism--ME; *Animals*; Cell Membrane Permeability; Endoplasmic Reticulum--metabolism--ME; Glycosides--metabolism --ME; Glycosylation; Microsomes, Liver--drug effects--DE; N-Acetylglucosaminyltransferases--metabolism--ME; Rats; *Transferases* (Other Substituted Phosphate Groups)--metabolism--ME

Enzyme No.: EC 2.4.1.- (N-Acetylglucosaminyltransferases); EC 2.4.1.150 (N-acetylglucosaminyltransferase); EC 2.7.8 (*Transferases* (Other Substituted Phosphate Groups)); EC 2.7.8.15 (UDPAcetylglucosamine-dolichyl-phosphate acetylglucosamine-1-phosphate *transferase*)

Chemical Name: Glycoproteins; Glycosides; Dolichol; Acetylglucosamine; Guanosine Triphosphate; N-Acetylglucosaminyltransferases; N-acetylglucosaminyltransferase; *Transferases* (Other Substituted Phosphate Groups); UDPAcetylglucosamine-dolichyl-phosphate acetylglucosamine-1-phosphate *transferase*

6/3,K/37 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)
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09331672 PMID: 1899070

Disruption of the Golgi apparatus by brefeldin A *inhibits* the cytotoxicity of ricin, modeccin, and Pseudomonas toxin.

Yoshida T; Chen C C; Zhang M S; Wu H C

Department of Microbiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799.

Experimental cell research (UNITED STATES) Feb 1991, 192 (2) p389-95
, ISSN 0014-4827 Journal Code: 0373226

Contract/Grant No.: GM28810; GM; NIGMS

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Record type: MEDLINE; Completed

Disruption of the Golgi apparatus by brefeldin A *inhibits* the cytotoxicity of ricin, modeccin, and Pseudomonas toxin.

We have studied the cytotoxicity of ricin in cells *treated* with brefeldin A (BFA), which dramatically disrupts the structure of the Golgi apparatus causing Golgi content and membrane to redistribute to the ER. BFA *inhibits* the cytotoxicity of ricin in Chinese hamster ovary, normal rat kidney, and Vero cells and abolishes the enhancement of ricin cytotoxicity by NH₄Cl, nigericin, swainsonine, and *tunicamycin* or by a mutation in endosomal acidification. BFA protects cells from the cytotoxicities of modeccin and Pseudomonas toxin, but has no effect on the intoxication by diphtheria toxin. Pretreatment of BFA does not protect cells from ricin *treatment* in the absence of BFA. Our results suggest that ricin, modeccin, and Pseudomonas toxin share a common pathway of intracellular transport from endosomes to the...

Descriptors: *ADP Ribose *Transferases*; *Bacterial Toxins; *Cyclopentanes--pharmacology--PD; *Cytotoxins--pharmacology--PD; *Golgi Apparatus--drug effects--DE; *Plant Lectins; *Virulence Factors; Alkaloids --pharmacology--PD; Ammonium Chloride--pharmacology--PD; *Animals*; Brefeldin A; Cell Line; Cytotoxins--antagonists and *inhibitors*--AI; Endocytosis--drug effects--DE; Exotoxins--pharmacology--PD; Kinetics; Lectins--pharmacology--PD; Mutation; Ricin--metabolism--ME; Ricin --pharmacology--PD; Swainsonine; *Tunicamycin*--pharmacology--PD

Enzyme No.: EC 2.4.2.- (ADP Ribose *Transferases*); EC 2.4.2.31 (toxA protein, Pseudomonas aeruginosa)

Chemical Name: Alkaloids; Bacterial Toxins; Cyclopentanes; Cytotoxins; Exotoxins; Lectins; Plant Lectins; Virulence Factors; *Tunicamycin*; Ammonium Chloride; Brefeldin A; modeccin; Swainsonine; Ricin; ADP Ribose *Transferases*; toxA protein, Pseudomonas aeruginosa

6/3,K/38 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08976620 PMID: 2159490

**Isolation of a crustacean N-acetyl-D-glucosamine-1-phosphate
transferase and its activation by phospholipids.**

Horst M N
Division of Basic Medical Science, School of Medicine, Mercer University,
Macon, GA 31207.

Journal of comparative physiology. B, Biochemical, systemic, and
environmental physiology (GERMANY, WEST) 1990, 159 (6) p777-88, ISSN
0174-1578 Journal Code: 8413200

Contract/Grant No.: GM-30952; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

**Isolation of a crustacean N-acetyl-D-glucosamine-1-phosphate
transferase and its activation by phospholipids.**

The N-acetyl-D-glucosamine-1-phosphate:dolichol phosphate *transferase*
from *Artemia* has been partially purified and characterized. The enzyme is
solubilized from crude microsomes using Triton X-100, and after detergent
removal appears to...

... GDP-mannose or dolichol phosphate mannose. The enzyme is rapidly
inactivated by exposure to several detergents, including Triton X-100 and
deoxycholate. The activity is *inhibited* by *tunicamycin* and by the
purified B2 homologue of this antibiotic. Other antibiotic *inhibitors*
such as diumycin and polyoxin D have little effect on the enzyme. Both the
microsomal and solubilized enzyme preparations are inactivated by 70% upon
treatment with phospholipase A2; activity may be restored by addition of
phospholipids. Following hydrophobic interaction chromatography on Phenyl
Sephadex, gel filtration chromatography on Sephadex CL-4B...

Descriptors: *Artemia--enzymology--EN; *Phospholipids--physiology--PH;
*Phosphotransferases--isolation and purification--IP; **Transferases*
(Other Substituted Phosphate Groups); *Animals*; Anti-Bacterial Agents
--pharmacology--PD; Chromatography, Affinity; Chromatography, Gel;
Detergents; Dolichol Monophosphate Mannose--isolation and purification--IP;
Enzyme Activation--physiology--PH; Larva--enzymology--EN; Microsomes
--enzymology--EN; Phospholipases A; Phosphotransferases--antagonists and
inhibitors--AI; Phosphotransferases--metabolism--ME; Solubility

Enzyme No.: EC 2.7 (Phosphotransferases); EC 2.7.8 (*Transferases*
(Other Substituted Phosphate Groups)); EC 2.7.8.15
(UDPacetylglucosamine-dolichyl-phosphate acetylglucosamine-1-phosphate
transferase); EC 3.1.1.- (Phospholipases A)

Chemical Name: Anti-Bacterial Agents; Detergents; Phospholipids; Dolichol
Monophosphate Mannose; Phosphotransferases; *Transferases* (Other
Substituted Phosphate Groups); UDPacetylglucosamine-dolichyl-phosphate
acetylglucosamine-1-phosphate *transferase*; Phospholipases A

6/3,K/39 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

08829556 PMID: 2513184

**ADP-ribosylation of the 78-kDa glucose-regulated protein during
nutritional stress.**

Leno G H; Ledford B E
Molecular and Cellular Biology and Pathobiology Program, Medical
University of South Carolina, Charleston 29425.
European journal of biochemistry / FEBS (GERMANY, WEST) Dec 8 1989,
186 (1-2) p205-11, ISSN 0014-2956 Journal Code: 0107600
Contract/Grant No.: CA30151; CA; NCI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Starvation of a *mouse* hepatoma cell line, Hepa, for any essential amino acid results in the mono-ADP-ribosylation of an 80-kDa protein, P80. The ADP-ribose acceptor...

... kDa glucose-regulated protein, GRP78. Starvation of Hepa cells for tryptophan or glucose stimulated the relative rate of synthesis, and the ADP-ribosylation of GRP78. *Inhibition* of N-linked glycosylation by *treatment* with *tunicamycin*, 2-deoxy-D-glucose or glucosamine stimulated the synthesis of non-ADP-ribosylated GRP78 up to sixfold with relatively little effect on its ADP-ribosylation. Both forms were identified in *mouse* liver, lung, heart, kidney, spleen and brain.

; ADP Ribose *Transferases*; Amino Acid Sequence; *Animals*; Carrier Proteins--isolation and purification--IP; Electrophoresis, Polyacrylamide Gel; Mice; Poly(ADP-ribose) Polymerases--metabolism--ME

Enzyme No.: EC 2.4.2.- (ADP Ribose *Transferases*); EC 2.4.2.30 (Poly(ADP-ribose) Polymerases)

Chemical Name: Carrier Proteins; Heat-Shock Proteins; Molecular Chaperones; molecular chaperone GRP78; ADP Ribose *Transferases*; Poly(ADP-ribose) Polymerases

6/3,K/40 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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06998310 PMID: 6741731

Ganglioside biosynthesis in rat liver golgi apparatus: stimulation by phosphatidylglycerol and *inhibition* by *tunicamycin*.

Yusuf H K; Pohlentz G; Schwarzmunn G; Sandhoff K
Advances in experimental medicine and biology (UNITED STATES) 1984,
174 p227-39, ISSN 0065-2598 Journal Code: 0121103

Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Ganglioside biosynthesis in rat liver golgi apparatus: stimulation by phosphatidylglycerol and *inhibition* by *tunicamycin*.

... the absence of any detergents, stimulated 6- and 20-fold, respectively, by phosphatidylglycerol. Other phospholipids like dolichyl phosphate, phosphatidylethanolamine and phosphatidylserine are also significantly stimulatory. *Tunicamycin* *inhibits* the synthesis of gangliosides GM2 and GM1 in isolated Golgi vesicles, but only in the absence of detergents. The dependence on phosphatidylglycerol and the degree of *inhibition* by *tunicamycin* of the synthetic activities are strictly dependent on the intactness of the Golgi vesicles: both phenomena become increasingly less evident when the vesicles are pelleted, and frozen and thawed several times, and completely disappear when the vesicles are

solubilized by the detergents or disrupted by ultrasonication. Furthermore, *tunicamycin* *inhibition* is reversible by increased concentration of phosphatidylglycerol. In pronase-*treated* Golgi vesicles, which retain full enzyme activity, both phospholipid-dependence and *tunicamycin* *inhibition* of the synthetic activity disappear completely. When freshly prepared Golgi vesicles are incubated with 125 microM UDP [3H]Gal for 10 min at 30 degrees...

... found to be transported into the vesicles at the rate of about 85 pmoles/mg protein/min, 92% of radiolabel remaining firmly bound with membrane. *Tunicamycin* *inhibits* this transport in a concentration-dependent manner. The results show that, while the mechanism of phosphatidylglycerol induced stimulation of the synthetic activity remains unclear, *tunicamycin* *inhibits* ganglioside biosynthesis by blocking the transport of the nucleotide sugar across Golgi vesicles and not *inhibiting* the *transferase* enzyme directly.

Descriptors: *Gangliosides--biosynthesis--BI; *Glucosamine--analogs and derivatives--AA; *Golgi Apparatus--metabolism--ME; *Liver--metabolism--ME; *Phosphatidylglycerols--pharmacology--PD; **Tunicamycin--pharmacology--PD; *Animals*; Detergents--pharmacology--PD; Golgi Apparatus--drug effects--DE; Kinetics; Rats

Chemical Name: Detergents; Gangliosides; Phosphatidylglycerols; *Tunicamycin*; Glucosamine

6/3,K/41 (Item 7 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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06132606 PMID: 6168561

Glycoprotein synthesis in lysolecithin-*treated* cells using sugar nucleotides as glycosyl donors.

Rudick M; Rudick V; Magie S; Jacobson E

In vitro (UNITED STATES) Feb 1981, 17 (2) p173-7, ISSN 0073-5655

Journal Code: 0063733

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Glycoprotein synthesis in lysolecithin-*treated* cells using sugar nucleotides as glycosyl donors.

The 3T3 cells were *treated* with 50 mu g/ml lysolecithin (LL) followed by the addition of exogenously supplied radiolabelled sugar nucleotides to serve as direct glycosyl donors. These were found to be 1.5 to 3.0 times more active than untreated cells in their glycosyl *transferase* activities depending on the particular sugar nucleotide used. Mannosyl *transferase* activity was not *inhibited* by 2-deoxyglucose or mannose-1-phosphate, indicating that the sugar nucleotide remained intact throughout the assay period. Preincubation of the cells with *tunicamycin* caused an 85% decrease in mannosyl transfer, which suggested that the normal pathway of glycosylation via lipid intermediates was still operable in the *treated* cells. Fractionation of control and LL-*treated* cells after incubation with UDP[3H]galactose revealed that only microsomal and cytosolic proteins from the *treated* cells were radioactive. Thus, intracellular labelling of permeabilized cells was allowed. About 80% of the radiolabeled product was glycoprotein in nature, based upon its solubilization...

; *Animals*; Cell Line; Cell Membrane Permeability; Lysophosphatidylcholines--pharmacology--PD; Magnesium--pharmacology--PD; Manganese--pharmacology--PD; Mice; *Tunicamycin*--pharmacology--PD

Chemical Name: Glycoproteins; Lysophosphatidylcholines; Nucleoside Diphosphate Sugars; Uridine Diphosphate Sugars; *Tunicamycin*; Uridine Diphosphate Galactose; Guanosine Diphosphate Mannose; Uridine Diphosphate N-Acetylglucosamine; Magnesium; Manganese

6/3,K/42 (Item 1 from file: 434)

DIALOG(R)File 434:SciSearch(R) Cited Ref Sci

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05101417 Genuine Article#: QN968 No. References: 765

Title: MELANIN - THE ORGANIZING MOLECULE

Author(s): BARR FE; SALOMA JS; BUCHELE MJ

Corporate Source: INST STUDY CONSCIOUSNESS,2924 BEVENUE

AVE/BERKELEY//CA/94705

Journal: MEDICAL HYPOTHESES, 1983, V11, N1, P1-140

Language: ENGLISH Document Type: REVIEW, BIBLIOGRAPHY

Research Fronts: 83-0250 001 (BACTERIAL CHEMOTAXIS AND SENSORY TRANSDUCTION; ROLE OF PROTEIN CARBOXYL METHYL *TRANSFERASES* IN BACTERIA AND EUKARYOTES)

83-0438 001 (RETINAL DEGENERATION IN PATIENTS WITH VITILIGO)

83-1314 001 (*HUMAN* AND RABBIT POLYMORPHONUCLEAR LEUKOCYTE RECEPTOR MODULATING FACTORS IN PATHOLOGY; EFFECTS OF FORMYL PEPTIDES, SERUM DERIVED CHEMOTAXINS, HISTAMINE, CALCIUM, COMPLEMENT, PH AND TEMPERATURE)

83-1356 001 (*INHIBITION* OF ORNITHINE-DECARBOXYLASE ACTIVITY BY ALPHA-DIFLUOROMETHYLORNITHINE AND POLYAMINE METABOLISM IN EUKARYOTIC CELL GROWTH AND CARCINOGENESIS; EFFECTS OF PUTRESCINE AND SPERMIDINE)

83-2106 001 (ROLE...

...MEMBRANES)

83-4127 001 (REGULATION OF ADENYLATE-CYCLASE COUPLED BETA-ADRENERGIC RECEPTOR SYSTEMS BY REGULATORY PROTEINS AND PERTUSSIS TOXIN; STRUCTURE, ACTIVATION AND DESENSITIZATION IN RAT, *MOUSE* AND OTHER MAMMALIAN CELLS)

83-4277 001 (IMMUNOREACTIVITY OF THE PITUITARY AND BRAIN RELATED BETA-ENDORPHIN, DYNORPHIN, ENKEPHALIN AND OTHER OPIOID-PEPTIDES)

83-4502 001 (ISOLATION AND SYNTHESIS OF PALLYTOXIN AND OTHER MARINE STEROLS)

83-5096 001 (ROLE OF EPIDERMAL GROWTH-FACTORS, TRANSGLUTAMINASE *INHIBITORS*, BACITRACIN AND OTHER FACTORS IN CELL PHYSIOLOGY)

83-5229 001 (EFFECT OF VITAMIN-A AND CHEMOPREVENTIVE RETINOLIDS ON SPERMATOGENESIS AND DIFFERENTIATION OF CULTURED CELLS)

83...

...OF ZINC, CADMIUM, NICKEL, LEAD, IRON AND MERCURY ON INDUCTION AND ACTIVITY OF MICROSOMAL HEME OXYGENASE IN RATS)

83-5681 001 (EFFECT OF RECOMBINANT INTERFERON *TREATMENT* ON *HUMAN* NATURAL-KILLER CELL CYTOTOXICITY)

83-5706 001 (SYSTEMATICS, BIOGEOGRAPHY, CLADISTIC ANALYSIS AND ASPECTS OF PHYLOGENETIC RELATIONSHIPS IN PATTERNS OF SPECIATION AND EVOLUTION)

83-5919 001...

...MODELS OF NON-LINEAR OPTICS AND INSTABILITIES IN CHEMICAL SYSTEMS)

83-7282 001 (PHOSPHOLIPID METHYLATION, RECEPTOR REGULATION, PHOSPHATIDYLCHOLINE SYNTHESIS AND ASSOCIATED STUDIES)

83-7519 001 (*INHIBITION* OF GLYCOSYLATION IN GLYCOPROTEIN BIOSYNTHESIS BY *TUNICAMYCIN* AND ITS EFFECT ON PROTEIN SECRETION)

83-7696 001 (IMPLICATIONS FOR READING COMPREHENSION OF VISUAL INFORMATION PROCESSING AND SEQUENTIAL EYE-MOVEMENTS IN THE READERS)

83-7917 001 (GENERATION OF OXYGEN RADICALS AND OTHER REACTIVE OXYGEN INTERMEDIATES BY *HUMAN* NEUTROPHILS AND POLYMORPHONUCLEAR LEUKOCYTES;

ROLE IN CYTOTOXICITY AND OTHER CELLULAR FUNCTIONS)
 83-8021 001 (CIRCADIAN-RHYTHMS, SLEEP AND DEPRESSION;
 AFFECTIVE-DISORDERS AND SUPPRESSION OF MELATONIN...
 ...DENSITY LIPOPROTEINS, LIPOPROTEIN-LIPASE AND CHOLESTEROL TRANSPORT)
 83-0824 002 (PROTEIN-KINASE, PHOSPHODIESTERASE, AND THE REGULATION OF
 CALCIUM VIA CALMODULIN MODIFICATION; MECHANISM OF ACTIVATION AND
 INHIBITION)
 83-0860 002 (RECEPTOR MEDIATED ENDOCYTOSIS AND ROLE OF COATED VESICLES
 IN PLASMA MEMBRANE RECYCLING; CLATHRIN AND OTHER PROTEIN VESICLE
 COMPONENTS)
 83-1075 002 (ADENOSINE...
 ...THE CATECHOLAMINES DOPAMINE AND NOREPINEPHRINE IN THE SUBSTANTIA-NIGRA
 AND BRAIN NEURONS OF THE RAT)
 83-8710 002 (CHARACTERIZATION OF THE ROLE AND FUNCTION OF *HUMAN*
 MACROPHAGES AND MONOCYTES)

6/3,K/43 (Item 1 from file: 35)
 DIALOG(R)File 35:Dissertation Abs Online
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01525900 ORDER NO: AADMM-12711
CONTROL OF O-GLYCAN BIOSYNTHESIS
 Author: TOKI, DALE JUNJI
 Degree: M.SC.
 Year: 1996
 Corporate Source/Institution: UNIVERSITY OF TORONTO (CANADA) (0779)
 Source: VOLUME 35/01 of MASTERS ABSTRACTS.
 PAGE 246. 178 PAGES
 ISBN: 0-612-12711-7

Descriptors: CHEMISTRY, BIOCHEMISTRY ; BIOLOGY, *ANIMAL* PHYSIOLOGY

The rate of incorporation of GalNAc into the glycoprotein by bovine colostrum UDP-GalNAc:polypeptide α -N-acetylgalactosaminyl-transferase (ppGA-T) was favoured when the hydroxyamino acid was Thr. Pre-existing sugars on the glycopeptide inhibited further glycosylation as did substituting other amino acids for Pro near the putative secondary glycosylation site.

The cDNA sequence corresponding to the cytoplasmic tail and transmembrane domain was replaced with a sequence encoding a cleavable insect protein signal sequence and the fusion protein was expressed in insect cells. Tunicamycin treatment, site directed mutagenesis and 5' deletion analysis confirmed the existence on N-glycans and emphasized their importance in maintaining the activity of C2GnT.

Upon ultraviolet irradiation at 360nm, the UV reactive substrate GAL β 1-3GalNAc α -p-nitrophenyl selectively inhibited C2GnT but not other glycosyltransferases. The inhibition could be prevented by substrate protection. GalNAc α -pNp at higher concentrations also inactivated UDP-Gal:GalNAc-R β 3-galactosyltransferase (Core 1 Gal-T ...

6/3,K/44 (Item 1 from file: 149)
 DIALOG(R)File 149:TGG Health&Wellness DB(SM)
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01915273 SUPPLIER NUMBER: 62891204 (USE FORMAT 7 OR 9 FOR FULL TEXT)
**Cerulenin, an Inhibitor of Protein Acylation, Selectively Attenuates
 Nutrient Stimulation of Insulin Release.**

Yajima, Hiroki; Komatsu, Mitsuhsa; Yamada, Satoko; Straub, Susanne G.; Kaneko, Tsuyoshi; Sato, Yoshihiko; Yamauchi, Keishi; Hashizume, Kiyoshi; Sharp, Geoffrey W.G.; Aizawa, Toru
Diabetes, 49, 5, 712

May,
2000

PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-1797

LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional

WORD COUNT: 5167 LINE COUNT: 00453

**Ceruleinin, an *Inhibitor* of Protein Acylation, Selectively Attenuates
Nutrient Stimulation of Insulin Release.**

... a sequel of cytosolic long-chain acyl-CoA accumulation, we examined if this reaction is engaged in nutrient stimulation of insulin release, using cerulenin, an *inhibitor* of protein acylation. In isolated rat pancreatic islets, cerulenin *inhibited* the glucose augmentation of (Ca.sup.2+)-stimulated insulin release evoked by a depolarizing concentration of (K.sup.+) in the presence of diazoxide and (Ca.sup.2+)-independent insulin release triggered by a combination of forskolin and phorbol ester under stringent (Ca.sup.2+)-free conditions. Cerulenin *inhibition* of glucose effects was concentration dependent, with a 50% *inhibitory* concentration ((IC.sub.50)) of 5 (micro)g/ml and complete *inhibition* at 100 (micro)g/ml. Cerulenin also *inhibited* augmentation of insulin release by (Alpha)-ketoisocaproate, a mitochondrial fuel. Furthermore, cerulenin abolished augmentation of both (Ca.sup.2+)-stimulated and (Ca.sup.2+)-independent...

...of protein kinases A and C, and mastoparan. Glucose oxidation, ATP content in islets, and palmitate oxidation were not affected by cerulenin. In conclusion, cerulenin *inhibits* nutrient augmentation of insulin release with a high selectivity. The finding is consistent with a prominent role of protein acylation in the process of (Beta...

...sub.ATP) channel-independent pathways of glucose signaling (15,16). Following up on this hypothesis, we examined the effects of cerulenin, a fungal antibiotic that *inhibits* protein acylation (17,18), on insulin release. We were interested in this drug because covalent protein acylation by LC-CoA is involved in vesicle translocation...

...could be responsible for the augmentation of insulin release via the (K.sub.ATP) channel--independent pathways. Accordingly, our expectation was that cerulenin, if it *inhibits* protein acylation in pancreatic (Beta)-cells as it does in other cells, would attenuate glucose augmentation of insulin release. In contrast, as stated above, the...normal conditions. As shown in Fig. 1, 16.7 mmol/l glucose caused a 10-fold increase in insulin release during 30 min, which was *inhibited* by cerulenin in a concentration-dependent manner. Cerulenin at 30 (micro)g/ml *inhibited* the glucose-induced insulin release by 87%. Basal insulin release in the presence of 2.8 mmol/l glucose was not affected by 30 (micro...

...sup.2+)).sub.i). The depolarizing concentration of KCl doubled the release (1st column vs. 6th column from the left in Fig. 1), and the *treatment* with 30 (micro)g/ml cerulenin had no effect on KCl-induced ((Ca.sup.2+)-stimulated) insulin release. Thus, cerulenin *inhibited* glucose stimulation of insulin release without perturbation of the (Ca.sup.2+)-responsive exocytotic machinery per se.

(Figure 1 ILLUSTRATION OMITTED)

Effects of cerulenin on...2.8 mmol/l glucose, and such release was augmented ~2-fold by 16.7 mmol/l glucose or 20 mmol/l KIC. Here again, *treatment* with 30 (micro)g/ml cerulenin abolished the glucose

augmentation of the (Ca.sup.2+)-independent insulin release and greatly attenuated (~90%) the KIC augmentation...

...insulin release induced by the combination of forskolin and TPA in the presence of low glucose (2.8 mmol/l) was not affected by the *treatment* with 30 (micro)g/ml cerulenin (4th column vs. 10th column from the left in Fig. 3).

(Figure 3 ILLUSTRATION OMITTED)

Concentration dependency of cerulenin...

...stimulated insulin release are shown. (Ca.sup.2+)-stimulated insulin release was evoked by 50 mmol/l KCl, and the glucose augmentation of it was *inhibited* by cerulenin in a concentration-dependent manner. The 50% *inhibitory* concentration ((IC.sub.50)) of cerulenin *inhibition* was 5 (micro)g/ml, and complete *inhibition* was observed at 100 (micro)g/ml. As can be seen in Fig. 4B, the concentration dependency of cerulenin *inhibition* was similar when its effect on the glucose augmentation of (Ca.sup.2+)-independent insulin release was examined.

(Figure 4 ILLUSTRATION OMITTED)

Even at a...

...glucose on both (Ca.sup.2+)-induced and (Ca.sup.2+)-independent (forskolin and TPA-induced) insulin release (15,16). Knowing that cerulenin is an *inhibitor* of palmitoylation, we examined the effects of cerulenin on the augmentation of insulin release by palmitate (Fig. 5). As shown in the left panel of...

...micro)mol/l forskolin, and 100 nmol/l TPA produced a 4-fold increase in insulin release in the absence of glucose. It was not *inhibited* by 30 (micro)g/ml cerulenin. As the other mode of potent non-nutrient secretagogue of insulin release, mastoparan, a wasp venom that directly activates...less in the presence of cerulenin at both the low and high concentrations of glucose.

DISCUSSION

In the present study, we found that cerulenin, an *inhibitor* of protein acylation (17,18), *inhibits* stimulation of insulin release by glucose, KIC, and palmitate. In contrast, cerulenin did not *inhibit* insulin exocytosis triggered by nonnutrient secretagogues, such as a depolarizing concentration of (K.sub.+), forskolin plus TPA, (K.sup.+) plus forskolin plus TPA, and mastoparan. Therefore, cerulenin is acting on the step commonly shared by the three nutrient secretagogues but not by the nonnutrient secretagogues. The concentration dependency of cerulenin *inhibition* of nutrient stimulation of insulin release is similar to the one reported for the drug-induced *inhibition* of protein acylation (17,18), supporting the idea that cerulenin is acting as an *inhibitor* of protein acylation under the experimental conditions used here. In fact, protein acylation may well be the key step common to glucose, KIC, and palmitate stimulation of the (Beta)-cell because anaplerotic metabolism of glucose and KIC raises cytosolic malonyl-CoA concentration, which leads to suppression of carnitine palmitoyl-*transferase* I activity and, eventually, accumulation of LC-CoA (6,7,9). Accumulation of cytosolic LC-CoA, in turn, will result in increased acylation of the...

...Regarding (Beta)-cell stimulation by palmitate, exogenous application is thought to cause protein palmitoylation, a well-documented example of acylation, which is expected to be *inhibited* by cerulenin.

In previous reports, it was shown that cerulenin has actions other than *inhibition* of protein acylation in various cells. These include apoptosis in cancer cells (29,30) and *inhibition* of fatty acid, cholesterol, RNA, and protein synthesis (17,18). In addition, increase in basal glucose oxidation, reduction in insulin-stimulated glucose oxidation,

and *inhibition* of acetyl-CoA carboxylase (18) by cerulenin were documented. Among these other actions of cerulenin, apoptosis, *inhibition* of RNA, and protein synthesis can be excluded as mechanisms of cerulenin *inhibition* of insulin release in our acute experimental conditions. Also, *inhibition* of fatty acid synthase by cerulenin is considered not responsible for the effect shown in this study because 1) the activity of the enzyme is...

...palmitate bypasses this step. Furthermore, we found that cerulenin had no effect on increased glucose oxidation and ATP content after exposure to high glucose. Thus, *inhibition* of glucose metabolism by cerulenin is most unlikely.

If cerulenin *inhibits* acetyl-CoA carboxylase in rat pancreatic islets, it is expected that cerulenin increases (Beta)-oxidation of fatty acid on one hand and blunts the suppressive...

...the fatty acid oxidation on the other. This is because acetyl-CoA carboxylase is a rate-limiting enzyme for malonyl-CoA production, and malonyl-CoA *inhibits* carnitine palmitoyltransferase I, an enzyme required for fatty acid incorporation into the mitochondrion for oxidation. However, we found that *treatment* of the islets by ...palmitate oxidation (in the presence of low concentration of glucose) and did not alter glucose-induced suppression of palmitate oxidation. This finding suggests that the *inhibitory* effect of cerulenin on insulin release in this study is not caused by *inhibition* of acetyl-CoA carboxylase.

To definitively establish that protein acylation is involved in nutrient-induced insulin release, a direct demonstration of protein acylation is required...

...be because the amount of protein palmitoylation is too small to detect by the method used. Further experiments are clearly needed.

In conclusion, cerulenin unequivocally *inhibits* stimulation of insulin release by glucose, KIC, and palmitate but not by nonnutrients. The finding strongly suggests a prominent role of protein acylation in the...

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...sup.+) channel-independent insulinotropic action of glucose. Diabetes 48:1543-1549, 1999

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DIALOG(R)File 149:TGG Health&Wellness DB(SM)

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01437135 SUPPLIER NUMBER: 13280213 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Pre-exposure to glucosamine induces insulin resistance of glucose transport and glycogen synthesis in isolated rat skeletal muscles: study of mechanisms in muscle and in rat-1 fibroblasts overexpressing the *human* insulin receptor.

Robinson, Katherine A.; Sens, Donald A.; Buse, Maria G.

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...insulin resistance of glucose transport and glycogen synthesis in isolated rat skeletal muscles: study of mechanisms in muscle and in rat-1 fibroblasts overexpressing the *human* insulin receptor.

TEXT:

...glucose enter this pathway as glucosamine-6-phosphate, we examined the effects of preincubation with glucosamine in isolated rat diaphragms and in fibroblasts overexpressing the *human* insulin receptor (HIR-cells). In muscles, pre-exposure to glucosamine *inhibited* subsequent basal and, to a greater extent, insulin-stimulated glucose transport in a time- and dose-dependent manner and abolished the stimulation by insulin of...

...pretreatment. In HIR-cells, which express GLUT1 and not GLUT4, basal and insulin-stimulated glucose transport were unaffected by glucosamine, but glycogen synthesis was markedly *inhibited*. Insulin-stimulated activation of protein kinases (MAP and S6) was unaffected, and the fractional velocity and apperent total activity of glycogen synthase was increased in glucosamine-*treated* HIR-cells. In pulse-labeling studies, addition of glucosamine during the chase prolonged processing of insulin proreceptors to receptors and altered the electrophoretic mobility of...

... action.

RESEARCH DESIGN AND METHODS

Rat muscle incubations. Male (50-80 g) Wistar BR rats Charles River, Wilmington, MA) were fasted overnight before experiments. The *animals* were decapitated, and the rat hemidiaphragms were dissected from the rib cage, weighed, and incubated as previously described in a rotating shaking water bath at...for label present in the extracellular space[12]. Under

these conditions, dGlc uptake is linear with time [12,14]. To ascertain that glucosamine did not *inhibit* dGlc phosphorylation, in some experiments the fraction of intracellular dGlc that was present as dGlc-6-P was measured as described previously[14].

HIR-cells...were pooled for each determination. Pellets were solubilized in 0.2 ml homogenization buffer (50 mM HEPES, 5 mM EDTA, 1% Triton-X100, and protease *inhibitors* [16]) at 4 [degrees] C for 30 min and centrifuged at 200,000 g for 60 min. A 10-[micro]l aliquot of the supernatant...

...described, and boiled in Laemmli's sample buffer[18]. Proteins were separated by SDS-PAGE (6% polyacrylamide) under reducing conditions. Gels were fixed, stained, destained, *treated* with [EN.sup.3 HANCE] (Dupont-NEN, Boston, MA), dried, and exposed to autoradiography film (X-Omat AR) with a Lightning Plus intensifying screen (Dupont...Peptide Synthesis Laboratory by Dr. Christian Schwabe. Crystalline, d(+)-glucosamine [multiplied by] HCl (tissue culture grade), myelin basic protein, and synthetic cAMP-dependent protein kinase *inhibitor* peptide (rabbit sequence) were from Sigma (St. Louis, MO). [[sup.S.35]]methionine and [[gamma].P.sup.32]ATP were from LCN (Costa Mesa, CA...

...from LC-services (Woburn, MA). Other reagents were purchased from previously indicated sources[12,15,18].

RESULTS

Glucose transport in muscles. Pre-exposure to glucosamine *inhibited* subsequent dGlc uptake by isolated hemidiaphragms in the absence and presence of insulin (Fig. 2). The *inhibitory* effect increased with the dose of glucosamine used (5-22 mM) and appeared time dependent. Although the [delta] insulin (insulin-stimulated minus basal dGlc uptake) was significantly *inhibited* after pre-exposure to 10 mM glucosamine for 1 (Fig. 2E and F) or 2 h (Fig. 2C), the fold stimulation by insulin ([delta] insulin...

...a 30-min incubation in medium devoid of glucose or glucosamine before the transport assay to remove potential transport competitors. Therefore, the glucosamine-induced transport *inhibition* likely reflects the effects of products of its metabolism. To assure that phosphorylation of dGlc was not rate limiting in glucosamine-*treated* muscles, the ratio of intracellular dGlc-6-P dGlc was measured at the end of the 15-min transport assay in studies designed exactly as...

...the initial phase of preincubation with glucose or glucosamine (followed by a period of insulin washout) to facilitate the transport of sugars[5]. However, the *inhibitory* effect of 10 mM glucosamine on subsequent basal and insulin-stimulated dGlc uptake was nearly identical whether or not insulin was included during the first...

...to media containing 5.6 mM glucose to assure cell viability during prolonged incubations. Because glucosamine competes poorly with glucose for transport[5,7], transport *inhibition* would likely have required much lower concentrations of glucosamine had it been added to glucose-free media. The marked increase in glucosamine's effects in...

...basal or insulin-stimulated dGlc transport by rat hemidiaphragms. This does not negate the results of Sasson et al.[25] in rat solei, because the *inhibitory* effect of glucose ...and we included a 30-min glucose-free incubation period before the transport assay. However, if pre-exposure to high glucose did have a residual *inhibitory* effect on dGlc transport, the data still indicate that glucosamine is a much more effective *inhibitor* of this process than equimolar glucose.

Glycogen synthesis and glycogen synthase activity in muscles.

Exposure to 10 mM glucosamine in the presence of 5.6...

...mM G-6-P) was not affected by insulin or glucosamine or both.

Insulin receptor number, kinase activity, and GLUT4 concentration in muscle. The marked **inhibitory** effect of glucosamine on insulin-stimulated glucose transport and metabolism suggested that insulin receptor number, subcellular distribution, or activation by insulin may be affected by...

...their in vivo activated condition (Fig. 4). To achieve full in vivo activation of plasmalemma insulin receptors, during the last 30 min of incubation insulin-**treated** muscles were exposed to 60 nM insulin [12].

Pre-exposure to glucosamine did not affect the number or the binding affinity of total insulin receptors solubilized from skeletal muscle. Scatchard analysis of equilibrium insulin binding showed typical curvilinear plots, which were identical in preparations from glucosamine-**treated** and from control muscles (Fig. 4A). Activation of the receptor kinase by insulin was assessed by measuring the insulin receptor catalyzed phosphorylation of a synthetic...

...4 mM) in the presence of 5.6 mM glucose, a glucosamine dose-dependent decrease in glycogen synthesis was observed (Fig. 5A). Note that glucosamine-**treated** and control cells were placed in identical media (5.6 mM glucose) during the 1-h glycogen synthesis assay, in the presence or absence of insulin. Although small decrements in basal glycogen synthesis were observed in cells that had been exposed to 2-4 mM glucosamine, the major effect was **inhibition** of insulin-stimulated glycogen synthesis, which declined by 50-80% after pre-exposure to 2 or 4 mM glucosamine, respectively. To assure that the **inhibition** of insulin-stimulated glycogen synthesis was not caused by the increased osmolarity of glucosamine-containing media, in some experiments control media were supplemented with equimolar sucrose, which did not affect basal or insulin-stimulated glycogen synthesis (data not shown).

We then examined whether glucosamine caused similar **inhibition** of glycogen synthesis at much lower concentrations, in the absence of glucose (Fig. 5B-E). Cell viability was unimpaired in glucose-free media with or...

...did not affect subsequent basal or insulin-stimulated glucose incorporation into glycogen, and inclusion of glucosamine (0.25-1 mM) caused only a modest (20%) **inhibition** of basal and insulin-stimulated glycogen synthesis (Fig. 5B). Incubation in glucose-free DMEM for 3-5 h (Fig. 5C and D) caused time-dependent... insulin and by 80% in its presence (Fig.

5D) compared with cells maintained in glucose (Fig. 5A). Addition of glucosamine to glucose-free media markedly **inhibited** both basal and insulin-stimulated glucose incorporation into glycogen in a time- and dose-dependent manner. After 5 h (Fig. 5D), 0.25 mM glucosamine caused 50% **inhibition** of basal and insulin-stimulated [[C.sup.14]]glucose incorporation into glycogen.

The enhanced labeling of glycogen after glucose deprivation (Fig. 5B-D) may have...

...approximately twofold higher than in cells that had been continuously exposed to glucose (Fig. 5A). Re-equilibration of cells with glucose before labeling decreased the **inhibitory** effect of glucosamine pretreatment; [K.sub.i] for glucosamine was 1 mM in Fig. 5E vs. 0.25 mM in Fig. 5D.

Glucose transport in HIR-cells. We examined whether glucosamine-induced **inhibition** of glycogen synthesis reflected **inhibition** of glucose transport. Table 1 suggests that this was not the case. In glucose-deprived HIR-cells under conditions where 0.25 mM glucosamine **inhibited** glucose incorporation into glycogen by -50% (Fig. 5D), dGlc uptake was unaffected by 0.25-1.0 mM glucosamine (Table 1).

Insulin (10 nM) caused...

...40%) stimulation of dGlc transport in HIR-cells, which was unaffected by pretreatment of the cells with glucosamine (Table 1).

[TABULAR DATA OMITTED]

Because glucosamine *inhibits* insulin-stimulated glucose transport in adipocytes (5) and in muscle (Fig. 2) but not in HIR-cells (Table 1), glucosamine-induced transport *inhibition* may be restricted to cells expressing GLUT 4. HIR-cells are fibroblasts and are expected to express GLUT1 but not GLUT4 (8). We confirmed this...

...data not shown).

Insulin activation of protein kinases in HIR-cells. The major effect of overnight exposure to glucosamine in the presence of glucose was *inhibition* of insulin-stimulated glycogen synthesis (Fig. 5A). Insulin activates glycogen synthase via glucose-mediated and -independent mechanisms (27). The latter pathway is catalyzed by activation...

...activated insulin receptor (30). In the experiments listed in Table 2, we examined whether overnight exposure to 4 mM glucosamine in the presence of glucose *inhibited* insulin stimulation of MAP kinase and S6 kinase activities.

[TABULAR DATA OMITTED]

After exposing cells for 5 min to insulin, the protein kinase activities of...

...of MAP kinase) or a synthetic peptide substrate of S6 kinase. Pre-exposure of cells for 18 h to 4 mM glucosamine (which caused 70% *inhibition* of insulin-stimulated glycogen synthesis, Fig. 5A) did not affect basal or insulin-stimulated protein kinase activities. Identical results were obtained when cells were stimulated...

...of glycogen synthesis is distal to activation of the protein kinase cascade by the insulin receptor.

Glycogen synthase activity in HIR-cells. Because glucosamine pretreatment *inhibited* glucose incorporation into glycogen at a step distal to glucose transport, we examined whether the activation state or total activity of glycogen synthase were affected...

...apparent additional activation of the enzyme that was, however, not statistically significant. Although the fractional velocity of the enzyme was increased in insulin-stimulated glucosamine-*treated* cells versus insulin-*treated* control cells, these differences were not significant. A marked discrepancy exists between the effects of glucosamine on glycogen synthase activity, which is significantly increased (Table...

...flux of glucose through the reaction in vivo, which is markedly decreased (Fig. 5). Decreased in vivo availability of UDP [multiplied by] glucose in glucosamine-*treated* cells could explain this discrepancy (31,32).

[TABULAR DATA OMITTED]

In vivo *treatment* of rats with glucosamine results in hepatic accumulation of UDP [multiplied by] N-acetylglucosamine and a concomitant decrease in UTP, UDP, UMP, UDP [multiplied by]...this was accompanied by labeling of fully processed [alpha]- and [beta]-insulin receptor subunits (135,000 and 95,000 [M.sub.r], respectively).

In glucosamine-*treated* cells, the decline in labeled proreceptors was much slower than in controls, and the appearance of [alpha]- and [beta]-subunits was concomitantly delayed. The difference was particularly striking after the 5-h chase (Fig. 6A). Delayed proreceptor processing in glucosamine-*treated* cells probably reflects abnormal glycosylation, because after 5 h a second (185,000 [M.sub.r]) proreceptor band appeared

in glucosamine-*treated* cells, and the electrophoretic mobility of the processed [alpha]-subunit was also increased (Fig. 6A).

Figure 6B illustrates the labeling pattern of multiple proteins, which...

...in the intensity of most radioactive bands during the 5-h chase. The overall pattern of labeled proteins was essentially identical in control and glucosamine-*treated* cells after 1 h. However, when examined after 3-5 h, several bands retained the label longer in glucosamine-*treated* cells than in control cells. The apparent increased half-life of these proteins may reflect the accumulation of inappropriately processed glycoproteins that are segregated in...

...of glucose transport in isolated adipocytes (5). It required the presence of glutamine (the amide donor for GFAT, Fig. 1) and was prevented by GFAT *inhibitors* such as azaserine. Glucosamine, which enters the pathway bypassing GFAT, mimicked the effect of glucose at much lower concentrations and was effective in the absence...

...transporters to translocate to the cell membrane (4).

Our data extend these findings to skeletal muscle and are consistent with the proposed interpretation. Glucosamine pretreatment *inhibited* basal and, to a greater degree, insulin-stimulated dGlc transport by muscles in a time- and dose-dependent manner. Insulin receptor number, tyrosine kinase activity, and GLUT4 protein expression were unaltered, suggesting that glucosamine pretreatment *inhibited* the distribution of GLUT4 to the cell membrane. In contrast to muscle and adipocytes, which express predominantly GLUT4, glucose transport was not affected by glucosamine *treatment* in HIR-cells (this study) or in vascular smooth muscle cells (7), although both cell lines exhibited striking responses to the *treatment* with respect to other parameters of metabolism or gene expression. The fact that both cell lines express GLUT1 and not GLUT4 supports the concept that...

...be restricted to GLUT4-expressing cells and may represent impaired GLUT4 recruitment to the cell membrane.

In both isolated muscles and HIR-cells, glucosamine pretreatment *inhibited* insulin-stimulated glucose incorporation into glycogen. In muscle, *inhibition* of glycogen synthesis was greater than that of glucose transport under the same conditions, suggesting that a step beyond glucose transport was also involved. In HIR cells, *inhibition* of glycogen synthesis was clearly distal to glucose transport and to activation of the kinase cascade by insulin, which were unaffected. It is unlikely that...

...shown). Under these conditions, glycogen synthase activity would be expected to be rate limiting for glycogen synthesis. It was therefore surprising that, in both glucosamine-*treated* muscles and in HIR-cells, glycogen synthase was activated. Glycogen synthase activity is regulated allosterically by G-6-P and covalently by phosphorylation/dephosphorylation at...

...does not affect the activity of the enzyme in vitro (data not shown). The increased in vitro activity of glycogen synthase in extracts from glucosamine-*treated* muscles and HIR-cells is unlikely to reflect copurified GlcN-6-P because 1) the latter is rapidly acetylated in vivo and is not expected...maximally stimulating concentration of G-6-P. Alternatively, because products of glucosamine metabolism appear to regulate the expression of several proteins (7,34-37), glucosamine *treatment* may have increased the concentration of glycogen synthase in HIR cells.

If glycogen synthase activity is increased and glucose transport and

hexokinase activity are unaltered in glucosamine-*treated* HIR cells, what causes the marked decrease in glucose incorporation into glycogen? The substrates of glycogen synthase are UDP [multiplied by] glucose and glycogen. UDP...

...less suitable for additional elongation. However, neither UDP [multiplied by] glucosamine nor glucosamine incorporation into glycogen have been demonstrated in vivo in livers of glucosamine-*treated* rats or in cultured cells, presumably because of the rapid conversion of GlcN-6-P to N-acetylglucosamine-6-phosphate (6,31,38). A more likely explanation may be limitation of glycogen synthesis by the reduced availability of UDP [multiplied by] glucose. The major metabolite that accumulates in glucosamine-*treated* cells or in livers of rats *treated* in vivo is UDP [multiplied by] N-acetylglucosamine (Fig. 1), and a concomitant depletion occurs of glycogen, UTP, UDP, and UDP [multiplied by] glucose. The...

...The low levels of UDP [multiplied by] glucose are thought to reflect in part trapping of UTP as UDP-N-acetylhexosamines and in part possible *inhibition* of G-1-P uridylyl *transferase* (31).

UDP [multiplied by] glucose, UDP-N-acetylglucosamine, and other UDP sugars are obligatory intermediates in the glycosylation and processing of glycoproteins both in the endoplasmic reticulum and in the Golgi system. Indeed, glucosamine is a known *inhibitor* of N-linked protein glycosylation, although the mechanism is incompletely understood (39). Our demonstration of delayed processing of the insulin proreceptor by glucosamine-*treated* HIR cells, as well as changes in the electrophoretic mobilities of the proreceptor and of the processed [alpha]-subunit, are consistent with altered glycosylation resulting...

...proreceptor processing when hepatocytes from rats with severe STZ-induced diabetes were pulse-labeled in unsupplemented DMEM (40). Although the concentration of glucosamine that rapidly *inhibited* proreceptor processing when added in the presence of 5.6 mM glucose was relatively high (10 mM), the limited transport of glucosamine, especially in the...

...a role in regulation of gene expression, e.g., the expression of glucose-regulated proteins Grp78 and Grp94 is induced both by hypoglycemia and by *inhibitors* of N-linked glycosylation (i.e., *tunicamycin*, 2-deoxyglucose and glucosamine; 36), and GLUT1 protein and mRNA content are increased in L6 myocytes in response to glucose deprivation or to glycosylation *inhibitors* (37).

In L6 myoblasts, the subcellular distribution and glycosylation of GLUT1 and GLUT4 is developmentally regulated (43), the latter may be important for their function...The rate-limiting enzyme controlling the metabolism of glucose to GlcN-6-P is GFAT, which has been cloned from bacteria, yeast, and from two *human* cDNA libraries (46,47). Yeast and mammalian GFAT activities are subject to allosteric *inhibition* by the product of the pathway, UDP-N-acetylglucosamine (6,46,47). In addition, GFAT expression appears to be negatively regulated by unidentified products of...

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Molecular biology of prion diseases.

Prusiner, Stanley B.

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PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English

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WORD COUNT: 7298 LINE COUNT: 00663

...ABSTRACT: not bacteria, fungi, parasites, viroids, or viruses. A review is presented of the molecular biology of prions and of the diseases they can cause in *humans* and *animals*. Scrapie is the *animal* disease caused by prions that has been most extensively studied; it can result in several conditions including bovine spongiform encephalopathy, which is currently wreaking havoc with the beef industry in Great Britain. The discovery of prion protein (PrP), which in *humans* consists of 253 amino acids, occurred in the early 1980s; the infectious component of the protein has also been identified (PrPSc). PrP genes are located on the short arm of *human* chromosome 20. The synthesis of PrPSc is described. Disorders in *humans* known to be caused by prions include kuru, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Straussler-Scheinker (GSS) syndrome; all are degenerative diseases of the central nervous system and can be transmitted to laboratory *animals*. Familial (inherited) variants of CJD and GSS also exist. Much of the current knowledge about prions has come from studying scrapie in laboratory *animals*. These findings are summarized and the many unresolved issues concerning prions, such as the ways prion infectivity increases, are discussed. Future research efforts will determine...

...entirely or whether other components are also present, and will attempt to identify the significant molecules' crystal structures and structures in solution. At present, no *treatments* for diseases caused by prions are known. Prenatal testing in families with histories of these disorders allows one way of controlling their genetic proliferation. (Consumer...

TEXT:

...vistas into fundamental mechanisms of cellular regulation and homeostasis not previously appreciated. Kuru, Creutzfeldt-Jakob disease

(CJD), and Gerstmann-Straussler-Scheinker syndrome (GSS) are all *human* neurodegenerative diseases that are caused by prions and are frequently transmissible to laboratory *animals* [2]. Familial CJD and GSS are also genetic disorders. Individuals at risk can often be identified decades in advance of central nervous system (CNS) dysfunction...

In addition to the three prion diseases of *humans*, four disorders of *animals* are included in the ensemble of prion diseases. Scrapie of sheep and goats is the most studied of the prion diseases. Bovine spongiform encephalopathy (BSE), transmissible mink encephalopathy, and chronic wasting disease of captive mule deer and elk are all thought to result from the ingestion of scrapie-infected *animal* products. BSE threatens the beef industry of Great Britain [5] and possibly other countries; the production of pharmaceuticals [6] involving cattle is also of concern...

...It is thought that BSE will disappear with the cessation of feeding rendered meat and bone meal, as has been the case in kuru of *humans*, confined to the Fore region of New Guinea and once the most common cause of death among women and children. Kuru has almost disappeared with...

...designated [Prp.sup.Sc].

Sequencing of molecular clones recovered from cDNA libraries that had been constructed from mRNA isolated from scrapie-infected Syrian Ha and *mouse* (Mo) brains showed that the Ha and MoPrP cDNAs encode proteins of 254 amino acids (Fig. 1) [20, 21]. Identical sequences were deduced from genomic clones derived from DNA of uninfected, control *animals* [20]. *Human* PrP consists of 253 amino acids [22]. Signal peptides (SPs) of 22 amino acids at the [NH.sub.2]-terminals are cleaved during the biosynthesis ...

...5] PrP 27-30 molecules per [ID.sub.50] unit [18]. (One [ID.sub.50] unit is the infectious dose at which 50% of the *animals* develop scrapie.) If <1% of the [PrP.sup.Sc] molecules contained an amino acid substitution or posttranslational modification that conferred scrapie infectivity, our methods would...38].

4) [PrP.sup.Sc] detected only in clones of cultured cells producing infectivity [50a].

5) PrP amyloid plaques are specific for prion diseases of *animals* and *humans* [34]. Deposition of PrP amyloid is controlled, at least in part, by the PrP sequence [71].

6) Correlation between [PrP.sup.Sc] (or [PrP.sup.CJD]) in brain tissue and prion diseases in *animals* and *humans* [82].

7) Genetic linkage between MoPrP gene and scrapie incubation times [55, 56]. PrP gene of mice with long incubation times encodes amino acid substitutions...

...PrP.sup.Sc] in the inoculum govern the "species barrier," scrapie incubation times, neuropathology, and prion synthesis in mice (71, 72).

9) Genetic linkage between *human* PrP gene mutation at codon 102 and development of GSS [3]. Association between codon 200 point mutation or codon 53 insertion of six additional octarepeats...

...copurification of [PrP.sup.Sc] and infectivity by immunoaffinity chromatography [38].

PrP Gene Structure and Expression

Localization of PrP genes to the short arm of *human* chromosome 20 and the homologous region of Mo chromosome 2 suggests that PrP genes existed before the speciation of mammals [39]. Hybridization studies demonstrated <0...

...that may function as a canonical binding site for the transcription

factor Sp1 [43].

Although PrP mRNA is constitutively expressed in the brains of adult *animals* [20], it is regulated during development. In the septum, PrP mRNA and choline acetyl *transferase* were found to increase in parallel during development [44]. In other brain regions, PrP gene expression ...chase period (Table 2) [49]. These observations are in accord with studies that show that [PrP.sup.Sc] accumulates in the brains of scrapie-infected *animals*, yet PrP mRNA concentrations remain unchanged [20].

Both PrP isoforms transit through the Golgi apparatus, where their asparagine-linked oligosaccharides are modified and sialic acid...
...for the synthesis of

[TABULAR DATA OMITTED]

protease-resistant PrP in scrapie-infected cultured cells [51]. This conclusion is based on results with the glycosylation *inhibitor* *tunicamycin* and with the expression of recombinant PrP with mutated asparagine-linked glycosylation sites. Experiments with transgenic mice may resolve whether unglycosylated [PrP.sup.Sc] is...

...a polymorphism in PrP was found at codon 171 (Fig. 2B) [46]; whether this polymorphism segregates with a Sip phenotype in Cheviot sheep is uncertain.

Human Familial Prion Diseases

CJD was believed to have a genetic basis when it was recognized that 10% of CJD cases are familial [2]. The discovery of the PrP gene (PRNP) in *humans* [22, 39] raised the possibility that mutation might feature in the *human* prion diseases; a point mutation at PrP codon 102 was found to be genetically linked to GSS syndrome (Fig. 2C) [3]. The codon 102 mutation... suggested that PrP gene mutations render individuals susceptible to a virus [36]. The putative scrapie virus is thought to persist in a worldwide reservoir of *humans*, *animals*, or insects without causing detectable illness. Yet one in [10.sup.6] individuals develop sporadic CJD and die from a lethal infection, whereas 100% of...

...gene germline mutations in patients and at-risk individuals cause familial prion diseases is supported by the experiments with transgenic mice described above. The transgenic *mouse* studies also suggest that sporadic CJD arises from the spontaneous conversion of [PrP.sup.C] to [PrP.sup.CJD] (a component of the prion that causes CJD) due either to a PrP gene somatic mutation or to a rare event involving modification of wild-type [PrP.sup.C].

Transgenic *Animals* and Species Barriers

The species barrier was discovered when scrapie prions were passaged between species; this is a stochastic process characterized by prolonged incubation times...

...that is observed for all subsequent passages, and transmission becomes a nonstochastic process. The species barriers is of practical importance in assessing the risk for *humans* of acquiring CJD after consumption of scrapie-infected lamb or BSE-infected beef.

To test the hypothesis that differences in PrP gene sequences might be...sup.C]-Pr[P.sup.Sc] heterodimers may be the rate-limiting step in the prion biosynthesis that determines scrapie incubation times (Fig. 4D).

In *humans* carrying point mutations or inserts in their PrP genes, mutant Pr[P.sup.C] molecules might spontaneously convert into [PrP.sup.Sc] (Fig. 4E). Although...Pr[P.sup.C] might extend our understanding of the pathogenesis of prion diseases and point to other macromolecules that participate in a variety of *human* and *animal* diseases of unknown etiology. Lessons learned from prion diseases may give insights into the etiologies, as well as the pathogenic mechanisms, of such common CNS...

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**Intracellular targeting and structural conservation of a
prohormone-processing endoprotease.**

Fuller, Robert S.; Brake, Anthony J.; Thorner, Jeremy
Science, v246, n4929, p482(5)
Oct 27,
1989

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RECORD TYPE: Fulltext TARGET AUDIENCE: Academic
WORD COUNT: 4034 LINE COUNT: 00371

... the protein are important in delivery of the enzyme to (or retention of the enzyme in) its normal intracellular compartment. We also identify a putative *human* homolog of Kex2.

We determined the sequence of 4118 nucleotides from a genomic clone containing KEX2 [4] and deposited these data in GenBank (accession number ...

...present in the cytoplasmic tail) [14]. Immunoprecipitated Kex2 was digested thoroughly with either endoglucosaminidase H (endo H) [15] or peptide: N-glycosidase F (PNGase) [16]. *Treatment* with either enzyme reduced the apparent molecular mass by 3000 to 5000 daltons (Fig. 1B), indicating that mature Kex2 contains a maximum of three N...

...transmembrane proteins [19], such Ser- and Thr-rich domains are modified by O-linked glycosylation. When Kex2 was detergent-solubilized from membrane fractions of cells *treated* with *tunicamycin* [to block N-linked glycosylation [20]], and then applied to a concanavalin A (Con A)--Sepharose column, 98% of Kex2 activity was retained. A significant... Kex2 from a marker enzyme in secretory vesicles (acid phosphatase) [24], but only partially resolves Kex2 activity from another marker enzyme ([alpha]-1,3-mannosyl *transferase*) though to reside in some Golgi cisterna [25]. Both the N- and O-linked oligosaccharides present on mature Kex2 carry [alpha]-1,3-linked mannose...

...alpha] factor processing in MAT[alpha] cells expressing either wild-type Kex2 or one of the three truncated proteins (Fig. 2B). A zone of growth *inhibition* (halo) is produced in a lawn of tester MATa cells only if mature [alpha] factor is secreted by MAT[alpha] cells. The MAT[alpha] strain...residues and 2 residues from the terminator linker [5]]. Tails as short as ten amino acids are competent to promote endocytosis through coated pits in *animal* cells [28]. Although the [delta]4 enzyme was detectably mislocalized (Table 1), its biological function did not seem to be impaired (Fig. 2B). However, a...

...acid cytoplasmic domain. This feature is noteworthy because Tyr residues are critical recognition elements for a set of proteins, called "adaptins," that are required in *animal* cells to link clathrin to the cytoplasmic tails of membrane proteins [28, 31]. The region of the Kex2 tail that contains both its Tyr residues...

...achieve pro--[alpha] factor processing (Fig. 2B).

The function of Kex2 and its true mammalian counterpart appears to have been highly conserved. Kex2 accurately processes *human* proinsulin at its Lys-Arg and Arg-Arg sites when this precursor is expressed in yeast [33]. Conversely, expression of KEX2 in processing-deficient mammalian cells results in specific cleavage of *mouse* pro-opiomelanocortin at Lys-Arg sites [34]. Finally, membrane preparations enriched in Kex2

properly cleave *human* proalbumin at its normal Arg-Arg processing site [35]. Therefore, we anticipated that the structural features of an authentic mammalian prohormone-processing endoprotease would closely resemble those of yeast Kex2.

A search of databases [36] revealed a partial sequence for a *human* gene product homologous to Kex2. The corresponding *human* gene (fur) lies immediately upstream of the fps/fes oncogene [37]. The sequence of 513 amino acids of the fur gene product ("furin") can be...

...identical to those observed in Kex2. The similarity between the putative catalytic domains and other regions of furin and Kex2 suggests that furin is a *human* prohormone-processing protease.

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REFERENCES...week intervals. After the first two boosts, subsequent boosts were made with protein that had been purified by chromatography on Sepharose CL-6B (Pharmacia). The *animals* were bled at the same time as booster injections were applied. Substantial Kex2-specific immunoreactivity was observed against purified fusion protein after the fifth bleed...

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